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Socioeconomic Distribution of Cervical Cancer

In Relation to Early Marriage and Pregnancy

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Socioeconomic Distribution Of Cervical Cancer

In Relation to Early Marriage and Pregnancy

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1964

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Introduction

Early marriage has been associated with cervical cancer in several studies (*1–5*). The incidence is high in the lower socioeconomic areas of most cities (*6–8*). The present study was undertaken to relate the etiology of cervical cancer to socioeconomic status and age at first marriage and first pregnancy. The data used are from the vaginal cytologic survey of Memphis, Tenn., which reached all levels of the city (*9–10*). The women are classified according to the socioeconomic status of the census tract in which they lived.

A case control approach is used because of the large number of women who were examined. Cases detected in the first screening are compared with a random 2.8 percent sample of women who participated in the survey but who did not have evidence of uterine cancer. Information on histologically confirmed cases of invasive and intraepithelial carcinoma of the cervix is presented separately.

Because evidence suggests that the epidemiologic distribution of squamous cell carcinoma differs from that of adenocarcinoma, cases are limited to the squamous type (*1, 6, 11*). Sixteen women having other histologic types of cancer were excluded from the study. The diagnostic criteria for intraepithelial carcinoma as used in Memphis are similar to those for squamous cell carcinoma except that no invasion of the underlying stroma is demonstrable although the lesion extends from the surface to the basement membrane.

The groups of women considered are those with confirmed cases of intraepithelial and invasive squamous cell carcinoma of the cervix and women whose cytologic findings were suspicious or positive with regard to malignancy (Papanicolaou classes 3–5), including those who either did not have biopsies or whose tissue studies failed to confirm the above-mentioned diagnoses (*12–15*).

To avoid repetition of cumbersome phrases, the following abbreviations will be used throughout for the three classes of abnormalities considered:

IEC for intraepithelial carcinoma of the cervix.
SCC for invasive squamous cell carcinoma of the cervix.
SPC findings for suspicious and positive cytologic findings.
SE for socioeconomic (as SE area of Memphis).

"Pregnancy history" will refer to age at first pregnancy or a response indicating that no pregnancy has ever occurred.

Historical Review

The incidence of invasive cervical carcinoma of the squamous cell type is exceedingly low in virgins (*16*). Some have doubted its existence (*17, 18*). This disease has not been reported in a female under 16 years of age (*11, 19–20*). Gagnon (*16*) has reported that no cases occurred in 13,000 nuns over a period of 20 years. During this time 14 carcinomas of the corpus uteri were found. In another study of 10,000 nuns, Towne (*21*) reported that three cases of the squamous cell type had occurred over a 20-year period and that three additional cases were found among 3,083 sisters who were seen in clinics.

There were 53 cases of the corpus uteri compared with 6 cervical cases. It would be of interest to know whether these religious orders accepted women who had been married and the virginal status of the patients and the other nuns. Others (*22–24*) have observed that the frequency of cervical carcinoma in nuns has been low in relation to other genital cancer. Taylor and co-workers (*25*) found that nuns had a lower mortality from all uterine and genital cancer than did the white general population of Massachusetts.

Wynder and associates (*1*), using interview data, found some cases of the squamous cell type in apparent virgins. They estimated that the risk of cervical cancer in white non-Jewish virgins was one fifth that for single nonvirgins. The risk for the latter was said to be similar to that for women marrying between the ages of 20 and 25. Stephenson and Grace (*26*) reported no virgins in 100 cases compared with 10 percent of controls. Rotkin (*4*), in a series of 100 patients and an equal number of controls, had 1 virgin patient compared with 5 virgin controls.

Single women have a lower incidence of cervical cancer than women who have married (*6*). Dorn and Cutler (*7*) have shown the age-standardized incidence in single white women to be 43 percent of that in the ever married. It is doubtful if the risk decreased for the nonwhite single women in this study because the incidence of uterine cancer in nonwhite women was greater in single than in ever married women. In New York City, however, the incidence of cervical cancer in single women was 61 percent of that in the ever married for the nonwhite races and about 50 percent for the white race (*27*). Petersen (*28*) found the proportion of unmarried women to be almost the same among cases of intraepithelial carcinoma and invasive carcinoma.

There are uncontrolled observations that pregnancy and common-law marriage are common in unmarried cervical cancer patients (*29*), and Peller (*30*) has reported that in two university hospital clinics in Vienna 74 percent of 173 single cervical cancer patients had been pregnant compared with 25 percent of 63 single women who had cancer of the corpus uteri and ovary.

Lombard and Potter (*2*) and several other investigators (*1, 3–5*) using hospitalized patients and controls have estimated at least a twofold risk of cancer among women who marry before age 20 compared with those who marry after age 20. However, in one study conducted in New York City (*31*) this factor was only slightly associated with cancer in non-Jewish white women and not at all in Jewish women. In California a slight excess of early marriages was noted for patients compared with controls of similar age and number of pregnancies. For both private and ward patients, it was found that the relationship persisted when the data were subdivided by the occupational status of the father and in ward patients when subdivided by the educational level of the patient (*32*). The highest estimated relative risk for those marrying before age 20 compared with after 20 was in the Jews of Israel (*31*). A relationship was present in London and in several cities of the United States. An association with early coitus has also been found (*1, 3, 4*). Dunham (*33*), however, found only a small difference in age at first intercourse for Negro patients in New York City when compared with controls.

An association between cervical cancer and having borne a child has been reported many times. Peller (*30*) also found an association between having one or more pregnancies and cervical cancer in married women when compared with patients having cancer of the corpus uteri and ovary. Stocks and Logan (*5, 34*) have reported that in England and Wales the risk of dying of cervical cancer was 23 percent greater in fertile women than in married women who have never borne children. Harnett (*35*) has conducted a study in which a series of cases were reported by the hospital registrars of London. He showed that approximately half as many married nulliparas were observed with cervical cancer as would have been expected on the basis of the number of married nulliparas observed in records of deaths from all causes. The expected numbers were adjusted for age. Petersen (*28*), reporting from the experience of

the Radium Institute in Copenhagen, found that 16.5 percent of women with intraepithelial carcinoma were nulliparous compared with an expected 32 percent for the general population, adjusted to the age of patients. Reagan and Hicks (*36*) found that in one hospital the percentage of patients who had never been pregnant was similar for intraepithelial and invasive carcinoma.

Most studies (*1–3, 5, 37*) have not found an association of cancer with number of pregnancies. An exception is a study (*38*) in which patients in one hospital, including both residents and nonresidents of the community, were compared with the population of the community. The positive association in this report could well be due to the lower SE status of the patients. No association was found between cancer and closely spaced pregnancies in one well-controlled study (*2*).

Gilliam (*39*) has shown that married cervical cancer patients had more pregnancies under 25 years of age than control groups who had skin or breast cancer or other disease. Lombard and Potter (*2*) studied age at first pregnancy but did not find it to be a significant factor. In one hospital study (*36*) it was reported that age at first pregnancy was similar for patients with cervical cancer and intraepithelial carcinoma. Wynder and co-workers (*1*) found a strong association with early pregnancy and were able to account for most of it by adjustment for age at first marriage. In view of the older age at marriage of infertile women, it was pointed out that the occurrence of a pregnancy was not independently associated with cervical cancer.

An early age at last pregnancy has been associated with carcinoma of the cervix (*2, 32*). In Wynder's study, however, the association was not independent of early marriage.

In several studies, marital instability has been found to be associated with cervical cancer. Lombard and Potter (*2*) found that 20.7 percent of their patients had been divorced or separated compared with 6.7 percent of the controls. Stocks (*5*) has shown that the widowed and divorced in England and Wales have a 25 percent higher death rate from cervical cancer than the married. Jones (*32*) was able to demonstrate a relationship between being separated or divorced and having cervical cancer for private patients who married after the age of 20. No significant association was shown for private patients marrying before age 20 nor for ward patients whether marrying before or after age 20. Matching the number of pregnancies probably acted as partial control for this factor, and his negative finding need not be accepted as evidence against a relationship. Wynder and co-workers (*1*) found a strong association between cervical cancers and being married two or more times. This was true regardless of the age at first coitus. Terris and Oalmann (*3*) found that 47 percent of patients had been married two or more times compared with 16 percent of controls. Petersen (*28*) found that a higher percentage of his patients with intraepithelial carcinoma had been divorced or separated than was so for the general population of Denmark. Other workers (*26, 31, 34, 40*) have also observed an association between cervical cancer and unstable marriages.

Terris (*3*) found that 54 percent of patients had had extramarital sexual partners compared with 26 percent of controls. Jones (*32*) did not find a difference in the percentage of patients and controls with less than five or more than five casual sexual partners. Using cervical cytology confirmed by surgical conization, Pereyra (*41*) found 14 cases of intraepithelial and 1 early invasive carcinoma in 601 prisoners. He estimated that this was six times higher than the prevalence of cases found in screening the women of Floyd County, Ga., by cervical cytology (*42*). The estimate was not adjusted for age. Pereyra characterized the prisoners as having had multiple diverse sexual experiences and hypothesizes that the high prevalence of cancer was due to an exogenous agent, possibly a virus, spread by promiscuity. Røjel (*17*) has shown that in Denmark there were four times as many known prostitutes among patients as among neighborhood controls.

An association between syphilis and cervical cancer has been established. Levin and co-workers (*43*) compared the proportion of

white cervical cancer patients and controls who were identified on the syphilis register of New York State. The controls were women with cancer of other sites. There were 36 cases, or 3.9 percent, identified on the syphilis register compared with 41, or 1.1 percent, of controls. Rojel (*17*) also matched case and control records with a syphilis register which was estimated to be over 92 percent complete. The controls had less syphilis in the upper than in the lower classes. There was a higher but constant percentage of patients with syphilis, however, irrespective of social class. This would suggest that in Copenhagen the behavioral causes of syphilis were similar to those of cervical cancer. No cancer was found in a gumma or chancre scar. Wynder (*1*) found age at first coitus could account for the estimated excess risk of cancer among patients with syphilis.

There is a consistent association between the incidence of cervical cancer and urban living. This has been noted in Connecticut (*44*), Iowa (*45*), and Denmark (*46*). Women in northern cities of the United States have a lower risk than those in the southern cities (*7*). According to Haenszel and Hillhouse (*27*), this north-south differential cannot be accounted for by differences in age at first marriage, frequency of circumcision, or prevalence of syphilis.

The incidence of cervical cancer is low in women under 20 years of age. After that it rises sharply until age 40. After age 50, as has been pointed out by Gilliam (*47*), the pattern differs by geographic area. In Memphis and to a lesser extent in Connecticut, the incidence continues to rise with age. In New York City and State it levels off, and in Denmark and Sweden it declines sharply (*47, 48*).

There are differences in the risk of cervical cancer between Negro and white women in the United States (*7, 27*), and American Indians have an intermediate mortality (*49*). These differences are thought to be related to environmental rather than genetic factors.

In 1902 Sinclair (*50*) recorded a clinical impression that "carcinoma of the cervix uteri occurs exclusively among the poor, the chronically overworked and underfed, among women, poor, profilic, harrassed, worried, drained by lactation, reposeless." Several studies have associated a low SE status with a high risk of cervical cancer. Incidence data from Copenhagen (*6*) and 10 large cities of the United States (*7*) have shown a SE gradient with cancer being most common in areas of the city with lower average rent and family income, respectively. There were relatively larger SE differences among the unmarried in Copenhagen when compared with women who were ever married.

Mortality statistics from England and Wales in 1930 showed a similar trend for all uterine cancer if the occupation of the husband was used to determine the social class of the wives. Mortality for single women was also associated with their occupational class (*51*). In 1950 the distribution of cervical cancer mortality for married women was also associated with the social class of their husbands. The wives of unskilled laborers (class V) had the greatest excess, 31 percent above average. The upper two classes were spared, having 76 and 77 percent of average, respectively (*52*).

Stocks (*5*) has found higher standardized mortality ratios for cervical cancer in the counties of England and Wales having the greatest mean number of persons per room. Higher standardized mortality ratios were also found for counties having a higher proportion of men in the lowest social classes (IV and V). Twelve of thirteen seaboard towns had more than a 13 percent increase in mortality when compared with all areas. Six of seven towns, predominately textile towns 20 years previously, had high relative mortality ratios. The uterine cancer death certificates used in the last two studies cited were queried when the site of origin was not designated.

Cohart (*53*) was unable to show a statistically significant association with area of residence in New Haven, although there were only 10 observed cases compared with 17 expected in the highest SE area. His method of classifying districts was complex and employed several indexes of social class, including the judgments of a sociologist (*54, 55*). Two thirds of the cases were reported to a

cancer register during the study period, and one third were reported at death. It is of interest that New Haven has a large Italian population and that census tracts in which this ethnic group predominates had below average median rentals (*8, 56*). In Buffalo some increase in the incidence of cervical carcinoma was noted for women living in lower SE areas of the city. The SE differences were increased by adjusting for marital status (*8*). The SE areas were made up of census tracts classified by median rent. Jones (*32*) found significant differences between patients and controls with regard to the father's occupation, separately for private and clinic groups.

In 1906 Vineberg (*57*) demonstrated that poverty is not necessarily associated with cervical cancer. He reported on 19,800 new patients seen between 1893 and 1906 in the Mt. Sinai Hospital gynecological clinic. Ninty-five percent of the patients were Hebrew women, mostly immigrants from Russia, Austria, or Poland, but only nine, or half of all cancer patients, were Jewish. Approximately 10 percent of all patients in this clinic had marked cervical lacerations. These women lived in the greatest squalor and privation, under the worst possible hygienic conditions. Many other studies have also found a favorable experience among Jewish women when compared with Gentiles (*58, 59*). The incidence in Israel is as low for Jews coming from Yemen as for those migrating from Europe. Since these groups differ in appearance and skin color, Hochman (*60*) concluded that genetic factors were not responsible for the resistance of Jewish women to cervical cancer. In New York City the estimated mortality is lower for foreign-born than for native-born Jews (*61*). Scapier and co-workers (*62*) found that only 6, or 18 percent, of their patients with intraepithelial carcinoma were Jewish women who, however, made up more than 60 percent of the women examined cytologically.

In attempting to account for the deficiency of cervical cancer in Jewish women, the well-performed circumcisions in their marital partners and absence of smegma have been suggested as protective factors. One hospital study showed an impressive association between uncircumcized husbands and cervical cancer in both white and Negro women (*1*). Other studies (*3, 32, 63*) have failed to show this. One found a negative association even after controlling for educational level and age at first coitus (*64*).

Plaut and Kohn-Speyer (*65*) produced skin malignancies in 4 of 278 mice by injecting horse smegma into skin tunnels. Both whole smegma and the nonsaponifiable fraction were active. Nonmalignant tumors also developed at the site of injection in four additional mice. Pratt-Thomas (*66–68*) has produced squamous cell carcinoma of the cervix in a small proportion of mice treated twice weekly with human smegma, but not by weekly applications. A more consistent yield was obtained if viable bacteria were present. In these experiments the content of dermoid cysts used as control material was not kept sterile and also produced cellular changes, including two cases of carcinoma. The data do show that squamous cell carcinoma of the cervix can be produced in mice by frequent application of human smegma. It is not clear what role microbiological agents are playing in these experiments. The applicability of these findings to human populations is unknown.

It has been demonstrated that men often do not know their own condition with regard to circumcision (*69–71*). This was not found to be true, however, of men examined in a cancer detection center in Los Angeles (*40*). The findings of Graham (*72*) that all of 15 cervical cancer patients correctly reported the circumcision status of their husbands would indicate that some wives accurately report this factor. Several workers (*69–71*) are in agreement that further investigations should be made which will include examination of the sexual partners of cervical cancer patients and properly selected controls.

Lombard and Doering (*73*) found lower mortality from uterine cancer for foreign-born women in Massachusetts. The rates for native-born of foreign parents were more than one third higher than for either foreign-born or native-born of native parents. Haenszel (*74*) has shown a lower mortality

from cervical cancer for the foreign-born of all countries of origin, except Canada and Mexico, when compared with total rates for white women in the United States.

A study which in some ways resembles the present study has recently been reported by Stern and Dixon (*40*). Cases of cervical cancer, intraepithelial carcinoma, and dysplasia were detected by vaginal cytology in a cancer detection center in Los Angeles. The criterion for a diagnosis of dysplasia was repeated cytologic abnormalities with or without histologic confirmation. The three classes of cervical abnormalities were compared with each other and with a sample of cytologically negative women. A number of factors were studied including race, circumcision of marital partners, utilization of sheath-type contraceptives, current age, age at marriage, current marriage status, whether of Jewish religion, and number of marriages and divorces. Each type of case showed the same associations, namely, a deficiency in Jews, an excess in women who had multiple changes in marital status, and no significant association with any of the other factors studied. Severity of lesions increased with age.

A study in New Orleans (*3*) found that cervical cancer patients had coitus much more frequently than gynecologic patient controls. They also had a larger proportion of divorces and early marriages. Another study in California (*32*) failed to find any association with frequency of intercourse in either clinic or private patients.

Newill (*61*) has estimated the mortality rates from cervical cancer for religious groups in New York City. Burial in a Jewish or Catholic cemetery was accepted as evidence of the respective religions, but persons buried in Protestant and independent cemeteries were distributed according to a formula derived from a sample. The population of New York City was also described by a sample survey. The rates for Jewish women were lowest. Protestants and Catholics had similar rates. Terris (*3*) found equal numbers of Baptists, other Protestants, and Catholics among patients and controls.

Stephenson and Grace (*26*) studied patients and controls who had cancer of sites other than the genitalia or breast. Fewer of the patients had experienced orgasm. Their husbands drank to excess and they more frequently expressed an aversion to sex. Jones (*32*) found that patients were less happy with marriage, received less sexual gratification, and were rated as having more psycho-physical stress than controls.

Studies of the frequency of uterine cancer in the families of cervical cancer patients and of matched controls have demonstrated that there was either a modest or no significant excess of cases in the cancer groups (*75–78*). In two studies of 200 patients each, uterine cancer was found in 1.4 percent of the mothers and aunts of controls and in 1.9 percent and 3.2 percent of these relatives of patients. In the study by Murphy (*76*), the difference was significant at the 2 percent level. Murphy has combined the results of these two studies and found that 2.5 percent of the mothers and aunts of cervical cancer patients had uterine cancer compared with 1.4 percent for controls. The difference was significant at the 3 percent level. The difference for sisters of patients and controls was significant at the 2 percent level in Brøbeck's study (*75*) although not for both studies combined. In the combined data, 1.8 percent of the sisters of cancer patients had uterine cancer compared with 0.6 percent for the control group.

No adequate studies of the role of poor obstetrical care have been reported. Data would be required on pelvic examinations, and obstetrical records would have to be reviewed. A history of unrepaired lacerations has been associated with the disease by one group using several types of controls (*2*). Histories of instrument deliveries were not incriminated in this nor at least three other studies (*1, 32, 39*). Long continued douching with coal tar derivatives was significantly more frequent in the Lombard and Potter cases (*2*) ; however, other studies (*1, 3, 32*) have failed to show differences.

Several studies (*1–3, 32*) have failed to establish the role of contraceptive practices. There was no significant association with abortions in at least four studies (*1, 2, 28,*

39). Jones (*32*) failed to find an association with genital hygiene, bathing, or coitus during pregnancy.

Large doses of estrogen administered over a long period of time will produce cervical cancer in mice (*79*). In humans, however, Jones (*32*) found no differences between patients and controls with regard to excretion of urinary estrogens. Dietary histories were similar with regard to the intake of riboflavin and thiamine. In one uncontrolled study (*80*), a severe deficiency of these vitamins had previously been found in cervical cancer patients which had produced liver dysfunction and inability to conjugate estrogens. The role of estrogens has not been established in the genesis of cervical cancer in humans.

Memphis Survey

The population of Shelby County, Tenn., consists almost entirely of white and Negro persons who were born in the United States. In 1950, 62.6 percent of the population of 482,393 were white and 37.4 percent were nonwhite. Between 1950 and 1960 the white population increased 32 percent and the nonwhite experienced a growth of 26.6 percent (*56*, *81*).

Earlier publications (*10*) have described the Memphis and Shelby County cytology project. The survey was carried out by the University of Tennessee and the National Cancer Institute with the cooperation of many local agencies and over 250 private physicians. Specimens were obtained by aspiration of the posterior fornix of the vagina. A total of 127,453 residents of Shelby County were examined at least once from July 1952 through June 1957. Many methods were used to encourage women to go to their private physicians or to one of the special temporary or permanent cytologic clinics for a cytology test. Private physicians were encouraged to send specimens from all adult female patients. Annual clinics were held in schools and establishments employing over 50 women.

Private physicians collected 61 percent of the initial cytologic specimens from white residents, but the City of Memphis clinics prepared 74 percent of such specimens from Negroes (*10*).

A total of 68 percent of white and 57 percent of Negro female residents over the age of 20 were examined. Among women who were 20 to 34 years old during the study, 89 percent were screened in each race; and among those 35 to 49 years of age, 72 percent of white and 52 percent of Negro women were examined. Screening was progressively less frequent in the older age groups, as approximately only 20 percent of women over 65 participated (*10*).

At the time the cytologic specimen was obtained, the doctor, nurse, or technician completed a brief history form (appendix). In the present study only entries recorded at the time of collecting the initial specimen were used. This decreased the danger of variation in quality of information on patients and controls, since the data were recorded before the cytologic findings were known.

Recommendations for further cytologic or tissue studies were based upon cytologic findings. When a slide was unsatisfactory for interpretation, a repeat examination was requested. When a slide contained atypical cells thought to represent benign epithelial abnormalities, the laboratory requested repeat specimens obtained by cervical pipette and scraping as well as by vaginal aspiration. Suspicious and positive findings were followed by recommendations for diagnostic tissue studies such as cervical biopsies, endocervical biopsies, or dilatation and curettage if a lesion of the uterine corpus was suspected.

Reports of cytologic findings and recommendations for further studies were made to physicians who had submitted specimens.

Women who had attended special cytologic clinics were advised of negative findings by mail. If repeat cytologic examinations or tissue studies were recommended for private patients and the physician could not get the patient to return, he often gave permission to a public health nurse to contact her. Clinic patients were routinely contacted by the public health nurse when repeat cytologic examinations or tissue studies were recommended. A followup clinic, where women were examined and biopsies obtained, was held weekly.

The survey director and pathologist (C. C. Erickson) made the diagnoses on all pathological specimens from the special followup clinic and city hospital. He also reviewed many of the slides which had been submitted to pathologists in private practice, especially in the earlier part of the survey. In other instances the diagnoses of other pathologists were accepted.

The private physician was telephoned after an appropriate interval to inquire whether he had made tissue studies. If a diagnosis of malignancy was reported, the doctor was asked whether cancer had been suspected and whether a biopsy would have been done without knowledge of the cytologic findings. If the specimen had been taken at the city hospital clinic, the hospital and outpatient records were reviewed. If cancer was one of the leading impressions, the case was classified as having been suspected before cytologic examination. In general, the term "unsuspected" was meant to describe cases which were diagnosed earlier than they could have been had no cytologic screening been carried out.

The Present Study

Because of the different racial incidence of cervical cancer and different social and economic conditions, all data are presented separately, by race. The 14 patients and 35 controls whose race had not been recorded were assigned to the race representing most of the households in the city block of residence as recorded in the 1950 census (*82*). This method of assigning race was accurate for 32 of 33 persons whose race subsequently had been recorded. The 17 patients and 34 controls whose ages had not been recorded are excluded from the present study. For most analyses, data for women under 20 years of age are not presented, primarily because there were no SCC cases and only one IEC case among them. However there were nine additional women under age 20 who had SPC findings.

One measure of the care with which histories were taken is shown by the number of persons for whom information was not

Table 1. Number and percent of patients and controls with incomplete histories, by type of information and race

Type of information	White patients[1]		Nonwhite patients[1]		White controls		Nonwhite controls	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Total women	331	100.0	186	100.0	1,708	100.0	764	100.0
Age at first pregnancy (or negative history of pregnancy)	17	5.1	3	1.6	83	4.9	14	1.8
Presence or absence of symptoms at time of screening	36	10.9	11	5.9	190	11.1	47	6.2

[1] Confirmed cases of squamous cell carcinoma and intraepithelial carcinoma.

Table 2. Frequency of pregnancy history omissions for controls, by source of referral and race[1]

Pregnancy history	White		Nonwhite		Total	
	Private physician	Other	Private physician	Other	Private physician	Other
Total controls	1,103	605	131	633	1,234	1,238
Unknown [2]	81	2	7	7	88	9

[1] $P < 0.001$ for both races combined.

[2] "Unknown" indicates either that no statement was recorded as to whether subject had been pregnant or that age at first pregnancy was not stated.

recorded. Table 1 shows the number and percentage of patients and controls with an incomplete history of pregnancy and presence or absence of symptoms, by race. Pregnancy history was not recorded for 5 percent of white and 2 percent of nonwhite patients and controls. The presence or absence of symptoms was unreported in 11 percent of white and 6 percent of nonwhite patients and controls.

Information, illustrated by history of pregnancy, was less complete for women whose first cytologic specimens were collected by private physicians (table 2). However, history of pregnancy was completed on 92.9 percent of controls from private physicians and on 99.3 percent of controls from other sources.

Socioeconomic Areas

Census tracts are geographic subdivisions of cities or urban areas. They were originally laid out in 1940; however, in Memphis, additional tracts have been created as new areas were incorporated. At the time they were set up census tracts were considered to be roughly homogeneous with regard to such characteristics as housing and income, education, religion, race, and type of occupation of the residents. In 1950 from 75 to 8,771 persons lived in individual census tracts in Memphis, and from one-tenth to 100 percent were members of the nonwhite race (*56*).

Data from the 1950 census are used to classify tracts with regard to SE status. Since the survey occurred over a span of 2 to 7 years after the census, significant changes in SE status may have occurred. This would be especially true for areas in which the population increased or decreased excessively. Table 3 shows the changes in census tract populations separately, by race, between the 1950 census and the special census of 1958. The white population of 17 tracts and the nonwhite population of 11 increased or decreased more than two-thirds between censuses. These residents are ex-

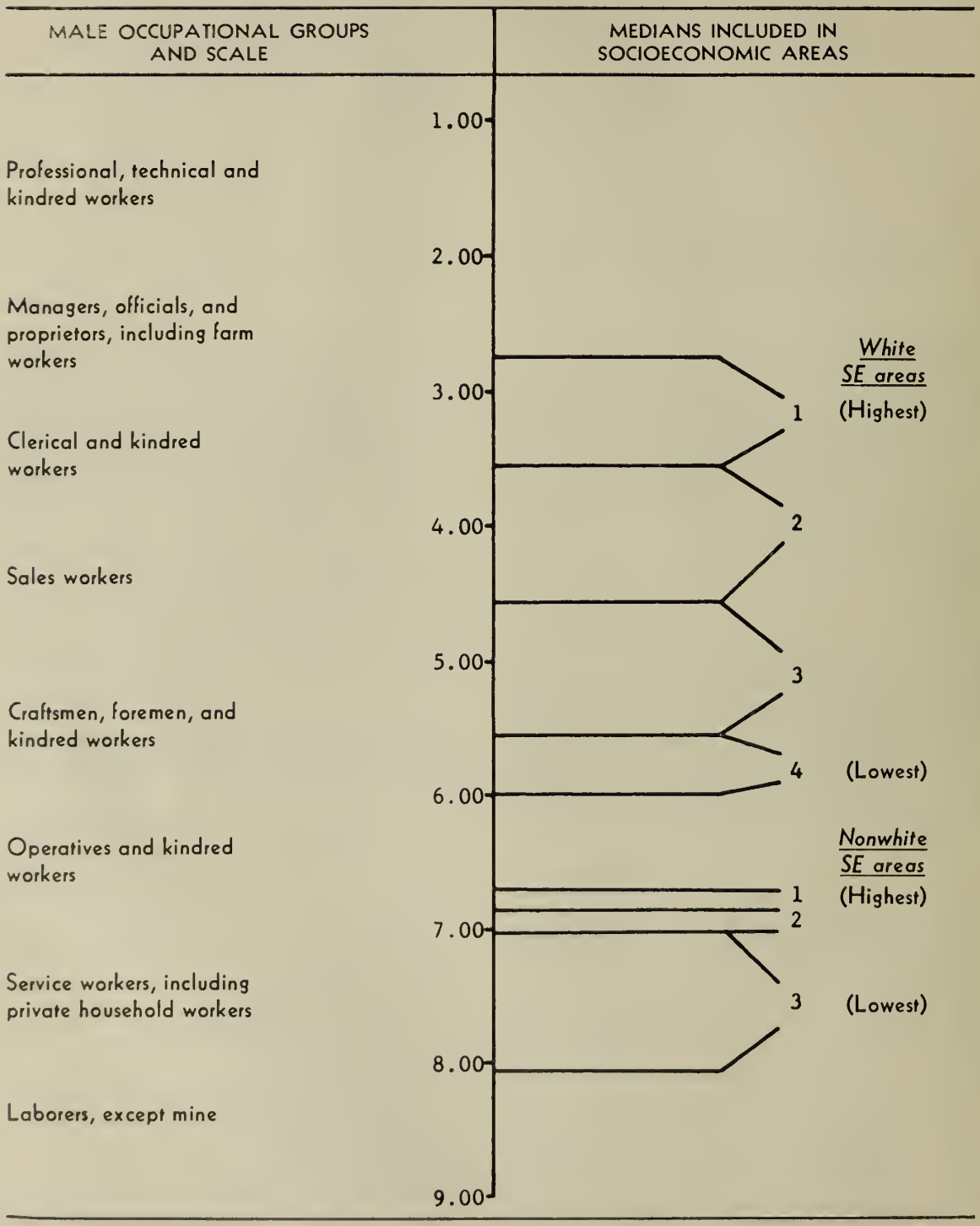
Table 3. Changes in census tract populations between 1950 and 1958, by race, Memphis, Tenn.[1]

Classification	Census tracts	
	White	Nonwhite
Total	90	90
Change in population:		
Increase of 2/3 or more [2]	10	9
Increase of 1/3 to 2/3	2	6
Increase or decrease of less than 1/3	49	35
Decrease of 1/3 to 2/3	12	6
Decrease of 2/3 or more [2]	7	2
Tracts with less than 250 white population in 1950 [2]	10	.....
Tracts with less than 250 nonwhite population in 1950 [2]	.....	32

[1] 1950 census and special census of Jan. 31, 1958. See references 56 and 83.

[2] Excluded from analyses using census tract classifications.

Figure 1. Range of median white and nonwhite male occupational groups in census tracts of each socioeconomic area, Memphis, Tenn., 1950



cluded from all tables using census tract data. Assuming that the changes occurred at a constant rate, the census tracts which are included would have had less than a one-third gain or loss of population in either race at the midpoint of the survey. Women were not tabulated if the tract in which they lived did not house at least 250 members of their race in 1950. Figure 1 shows each type of exclusion. Many analyses do not depend upon classification by census tracts. For these, the cases and controls living in all 98 tracts which were part of the city in 1956 are included. Residents of Memphis made up about 80 percent of the population of Shelby County, which was the unit of study in previous publications from the Memphis survey.

For most characteristics, census publications give data for all races combined and for the nonwhite race separately. The characteristics of white persons living in a census tract were obtained by subtracting the nonwhite from the total data. For tracts with fewer than 250 nonwhite persons in 1950, data were not published separately, and it was necessary to use the data for all races combined to classify the white population. The error associated with this procedure should be small, since the average white population of a census tract was 2,063, and few nonwhite persons were included erroneously.

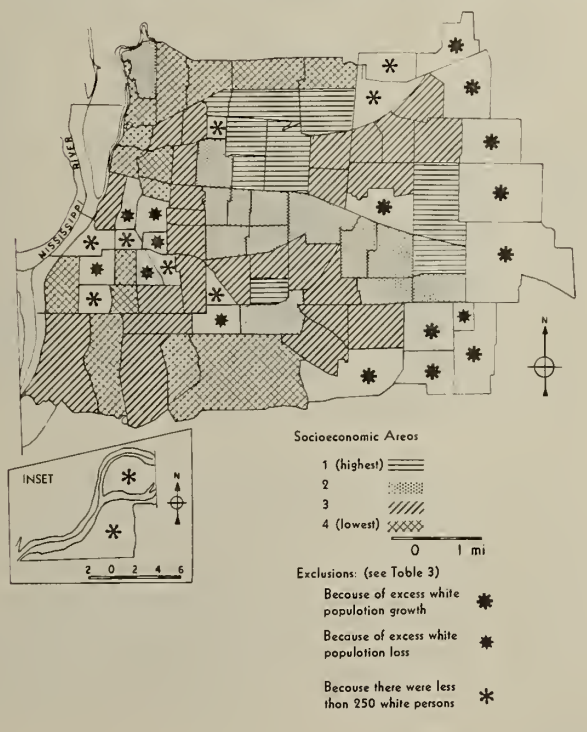
Social class, or social stratification, is thought to be a useful concept in epidemiology because it relates to many behavioral and environmental factors. If a disease can be related to social class, it is still necessary to demonstrate the reason or reasons for the association. There is some evidence indicating that the best single measure of social class is occupational level (*84*). For this reason our data for SE areas were based upon occupations. It is not clear, however, when using census tract data, whether there is any real advantage of a scale based upon occupation rather than housing quality, because these factors are well correlated.

The present study bases its classification of census tracts upon the employed males over 14 years of age who were tabulated by major occupational group, census tract, and race (*56*). The SE ranking of the U.S. Bureau of the Census is used. The service worker and private household worker groups are combined because very few males were in the latter group. A numerical range of values (fig. 1) has been assigned to each major occupational group. The median values on this scale have been calculated for each census tract separately, by race. If the number of employed males in each occupational group is represented as O_1 to O_8, O_k as the number in the group in which the median occurs, X_k as the numerical value at the division point between this group and the preceding group, and n as the number of employed males in the census tract, the

$$\text{median} = X_k + \frac{\frac{n}{2} - O_1 - O_2 - \ldots - O_{k-1}}{O_k}$$

Census tracts are combined to establish four arbitrary SE areas. The areas were chosen to assure adequate numbers of controls in each category. The division points which fall in the middle of major occupational groups emphasize the fact that the

Figure 2. White socioeconomic areas and excluded census tracts, Memphis, Tenn., 1950



SE areas are subdivisions of a continuous scale. Figure 2 shows the areas together with the exclusions previously described.

There were appreciable differences in the percent distribution of occupations of white males living in the four SE areas (fig. 3). This indicates some degree of success in subdividing the city into geographic areas having different SE levels.

The professional, technical, and kindred workers and the managers, officials, and proprietors comprised 51 percent of SE area 1 (highest) and 13 percent of area 4 (lowest). Craftsmen, foremen, operatives, and kindred workers comprised 17 percent of area 1 and 60 percent of area 4. Service workers and laborers comprised 4 percent of area 1 and 11 percent of area 4.

In contrast, the occupations of nonwhite males living in the three so-called SE areas show no substantial differences. Occupations above craftsmen and kindred workers comprised only 9.7 percent of area 1 and 8.3 percent of area 3. Service workers and laborers comprised 40 percent of area 1 and 54 percent of area 3. Therefore, all data pertaining to the census tract method of classification of nonwhite persons are not presented because considerable inter-census tract variation is necessary to establish significant associations by this method of group classification.

Selection of Control Sample

The comparison, or control group, consists of a 1-in-36 random-start systematic sample of resident women who were examined and were not found to have evidence of malignant uterine disease by the cytologic and tissue examinations performed during the survey. The records were in alphabetic order when the systematic sample was drawn. Table 4 shows the distribution of controls by age group and race.

Table 5 provides evidence that all white SE areas are well represented in the survey. The white controls, essentially a random sample of survey participants living in Memphis, are compared with the white female

Figure 3. Percent distribution of males by race, occupation, and socioeconomic area based on median male occupations in census tracts, Memphis, Tenn., 1950

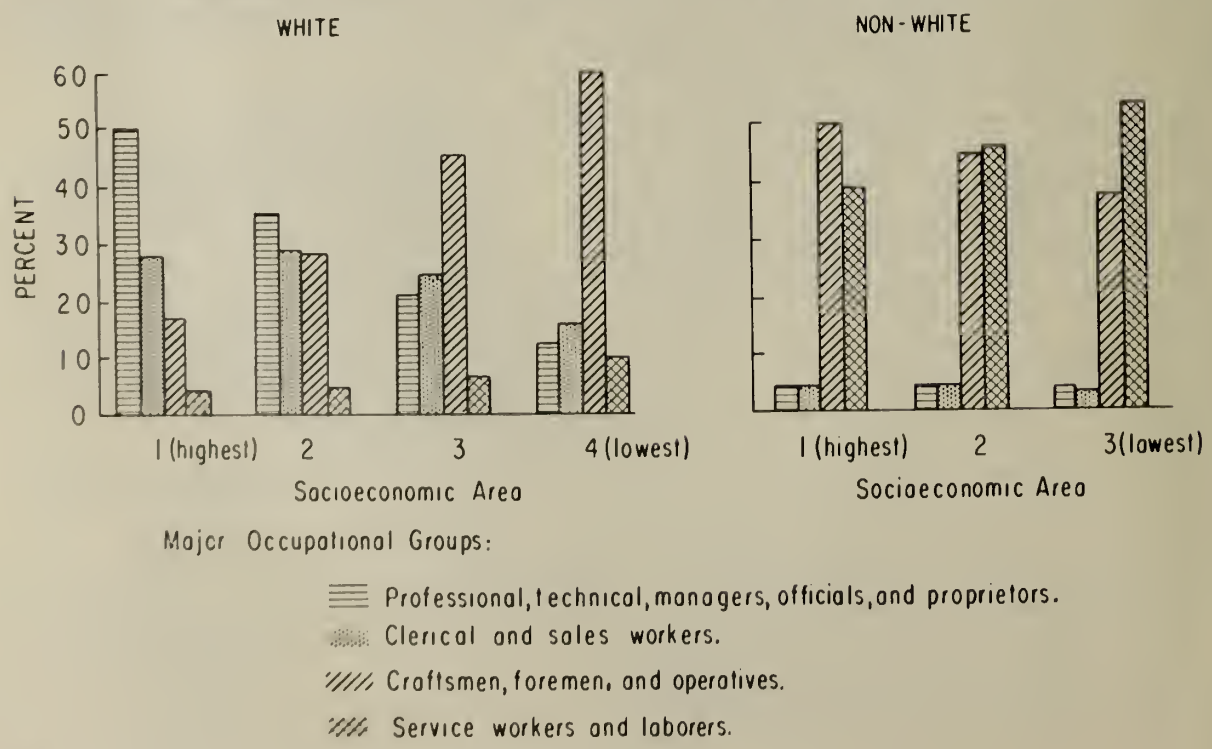


Table 4. Number and percent distribution of controls, by age group and race

Age group	White		Nonwhite	
	Number	Percent	Number	Percent
Total.	1,708	100.0	764	100.0
20–24.....	270	15.8	191	25.0
25–34.....	592	34.7	243	31.8
35–44.....	383	22.4	160	21.0
45–59.....	341	20.0	136	17.8
60 and over.	122	7.1	34	4.4

population of Memphis with regard to the SE area of residence. Comparisons are made within age groups as well as for all ages combined. There is slight overrepresentation of the upper SE area for all ages over 25.

Selection of Cases

One of the most serious defects of cross sectional and retrospective studies, from the viewpoint of drawing etiological inferences, is the difficulty of assessing biases. When a random selection of individuals to be screened cannot be made, volunteer bias may occur if persons with symptoms related to a disease are more likely to be examined than are those without symptoms. Similarly, the medical practitioners in a community may submit specimens more frequently when patients have certain signs or symptoms. There is a greater risk of such selection when a survey is conducted over a period of years as compared with a shorter interval of calendar time.

In the following paragraphs we discuss the method used in selecting cases which, in our opinion, reduces the possibility of bias. We also examine the data for evidence of bias not only by volition of the patient or physician in obtaining the initial specimen but also by failure to obtain tissue studies and by variation in the average duration of disease. The proportion of population screened differed by age and race. Since age adjustments are made and the data are kept separately by race, these differences should not in themselves create biases with regard to other characteristics to be studied.

Table 5. Number and percent distribution of white controls and white female population for each socioeconomic area, by age group

Socioeconomic area	Age group 20–24		Age group 25–34		Age group 35–44		Age group 45–59		Age group 60 and over		Total	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Controls: Total.....	205	100.0	365	100.0	286	100.0	289	100.0	104	100.0	1,249	100.0
1 (highest)..	26	12.7	62	17.0	53	18.5	59	20.4	19	18.3	219	17.5
2.....	43	21.0	84	23.0	78	27.3	84	29.1	34	32.7	323	25.9
3.....	105	51.2	164	44.9	116	40.6	121	41.9	42	40.4	548	43.9
4 (lowest)...	31	15.1	55	15.1	39	13.6	25	8.6	9	8.6	159	12.7
White female population:[1] Total.....	9,656	99.9	16,148	100.0	15,959	100.0	20,076	100.0	15,948	100.1	77,787	100.0
1 (highest)..	1,250	12.9	2,195	13.6	2,634	16.5	3,616	18.0	2,596	16.3	12,291	15.8
2.....	2,435	25.2	3,721	23.0	4,030	25.2	5,703	28.4	5,097	32.0	20,986	27.0
3.....	4,544	47.0	7,653	47.4	7,097	44.5	8,212	40.9	6,265	39.3	33,771	43.4
4 (lowest)...	1,427	14.8	2,579	16.0	2,198	13.8	2,545	12.7	1,990	12.5	10,739	13.8

[1] Estimated for January 1, 1955, by straight-line extrapolations between 1950 and 1958 censuses.

All patients known to have had uterine cancer before the first cytologic examination are excluded because their representativeness is questionable. The cases of uterine cancer coming to medical attention in Shelby County between January 1, 1950, and the end of the cytologic survey had been identified and matched with the file of cytologic examination forms. Subsequent to January 1, 1952, patients were not identified if they were seen by private physicians only and were unknown to hospitals, oncology clinics, X-ray therapy centers, or pathologists.

A suspicious or positive cytologic examination was required of each patient before or on the day that her tissue was studied. To avoid counting nondiseased women among the definite cases, histologic confirmation was required within 18 months after the initial smear. In measuring prevalence of SCC and IEC cases in the present study, it was assumed that progression or regression did not occur between the initial smear and confirmation by tissue studies. Appendix table 1 describes the distribution of intervals between initial smear and final diagnosis. The date of final diagnosis is the date the pathologic specimen was received. The patients whose cases were diagnosed within 3 days of the initial smear are thought, in most instances, to have had a clinically abnormal cervix and to have had biopsies at the time of taking the cytologic specimen.

IEC patients had symptoms slightly more often than controls. However, appendix table 2 shows that symptoms were reported for only 16 percent of white IEC patients compared with 11 percent of controls. In the nonwhite race 12 percent of the IEC patients were reported to have symptoms compared with 9 percent of controls. Furthermore, since the physical findings usually are not characteristic of cancer, significant bias in this group is unlikely.

Appendix tables 3 to 5 support the view that no important biases occurred with regard to the major variables of this study, which are pregnancy history and SE area of the white race. The percentage of SCC patients and controls reporting vaginal symptoms did not vary significantly among pregnancy history groups or SE area nor did the proportion of controls reporting symptoms vary significantly by age. As might be expected, symptoms were more frequently reported in older SCC patients although the excess was not statistically significant.

The possibility of bias in SCC cases still exists. For some analyses the data on women reporting no symptoms were studied separately, as generally these data would not be biased. However, limiting the data to the women without symptoms leaves relatively few SCC cases for study, since 40 percent of white patients reported vaginal symptoms and no record had been made for 15 percent as to the presence or absence of symptoms. In the nonwhite race, 53 percent of SCC patients reported symptoms, and the status of 9 percent was unknown.

Another way to assess whether significant bias occurred for SCC cases is to examine the data by source of referral (app. tables 6–8). Sources differed with regard to observed and age-adjusted expected IEC and SCC cases among white women. Much of the difference disappeared, however, when expected cases were obtained by adjusting for age and pregnancy history. The West Tennessee cancer clinic provides diagnostic services to the medically indigent, taking over a function which, for other persons, would be carried out by private physicians. In the nonwhite race, 16 cases, were observed from this clinic compared with less than 1 case expected after adjustment for age. These 16 cases are included in the present study because it is felt that most nonwhite persons screened were also medically indigent and that the control sample would be appropriate as a comparison group. This is consistent if symptomatic private patients are included, and they are. There were only minor differences among the other sources of referral with regard to observed and age-adjusted expected IEC and SCC cases. In other words, age could account for the variation in prevalence of cancer among nonwhite women classified according to source of referral, and age and pregnancy history could account for such variation among white women. This was true for

IEC as well as SCC cases. From these findings it would seem that, in general, the participating physicians and clinics were doing routine screening regardless of the presence or absence of signs or symptoms.

It is thought that excluding cases suspected by the physician would create a bias related to SE status. An unknown but probably significant number of women went to the offices of physicians for cytologic examinations, and in the process of obtaining histories and specimens, cancer was suspected. No comparable exclusions can be made for the sources of referral where pelvic examinations were not made; consequently, we are including suspected cases in our analysis. No doubt some women went to clinics or physicians because of symptoms related to cancer. One of our tasks is to evaluate the effect of this group of women upon the findings of the present study.

One would like to have a precise measure of the sensitivity of vaginal cytologic screening in Memphis. It is not possible to obtain this, in any series which includes cases detected primarily by the test which is to be evaluated. However, we have studied the cases of patients whose tissues were received in the pathology laboratories within 3 days of the initial smear. It is believed that most of these cases were detected primarily by biopsy. The smear was unsatisfactory for interpretation in 5 of 71 SCC cases and in 2 of 12 IEC cases. The initial cytologic specimen was suspicious or positive in 57 (86 percent) of the 66 remaining SCC cases and in 8 of 10 IEC cases. Five of the nine remaining SCC cases displayed atypical cells as did one of the two IEC cases. With repeat cervical and vaginal smears, some of the unsatisfactory and atypical cases probably would have had suspicious or positive findings, increasing the sensitivity of the screening program as opposed to the single cytologic examination. Repeat cytologic specimens were obtained from 53 percent of white and 56 percent of nonwhite controls who had had an unsatisfactory or atypical initial smear.

A screening survey which requires confirmation by followup examinations has another possibility of bias. This is the differential undercounting of cases because of failure to perform such examinations. To evaluate this possibility, the number of women with SPC findings was estimated. This group included all IEC and SCC cases, other types of cervical carcinoma, and probable IEC, together with a 50 percent terminal digit sample of women having atypical changes, findings negative for cancer, carcinoma of the corpus uteri, or having no tissue study which included the squamocolumnar junction. The total numbers of women with SPC findings are estimated by doubling the numbers in the categories which were sampled and adding these to the groups which were not sampled. Appendix tables 9 to 11 give these estimates together with estimates of the number of patients who did not have biopsies, by race, age group, age at first pregnancy, and SE area. Significant differences are present in the proportion not having biopsies, by age and race but not with regard to pregnancy history or SE area.

Prevalence studies may be biased if the mean duration of disease varies among subgroups. In this situation a higher prevalence in some groups could be produced by a longer mean duration of the disease. In the present study we are interested in the mean duration before diagnosis inasmuch as we have excluded previously diagnosed cases. This possibility of bias is considered in appendix tables 12 to 14 by showing the clinical stage for white patients by age group, age at first pregnancy, and SE area. There were more patients in advanced stages in the nonwhite than in the white race. This is consistent with the presurvey finding that white patients were diagnosed more frequently in stage I than were nonwhite patients (*10*). However, the ratio of stage 0, or IEC, to stage I is the same for each race. The distribution by stages did not vary significantly among the subgroups listed except by age and race.

The specificity of the cytologic screening may be estimated by determining the number of women with SPC findings who had tissue studies and, of these, the proportion diagnosed as having either IEC or SCC cases.

Table 6. Percent distribution of histopathologic diagnoses for patients with suspicious or positive cytologic findings, by age group and race[1]

Age group	Squamous cell carcinoma of cervix		Intraepithelial carcinoma of cervix		Negative and atypical tissues[2]		Other[3]		Total cases	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
White										
Total	138	19.8	193	27.8	304	43.7	60	8.6	695	99.9
20–24	0	0	7	11.9	46	78.0	6	10.2	59	100.1
25–34	20	9.6	71	34.0	100	47.8	18	8.6	209	100.0
35–44	33	18.4	63	35.2	76	42.4	7	3.9	179	99.9
45–59	45	27.4	35	21.3	66	40.2	18	11.0	164	99.9
60 plus	40	47.6	17	20.2	16	19.0	11	13.1	84	99.9
Nonwhite										
Total	93	18.4	93	18.4	260	51.4	60	11.8	506	100.0
20–24	1	1.1	11	12.6	64	73.6	11	12.6	87	99.9
25–34	9	5.7	40	25.5	94	59.9	14	8.9	157	100.0
35–44	25	24.8	29	28.7	42	41.6	5	5.0	101	100.1
45–59	33	32.7	11	10.9	42	41.6	15	14.9	101	100.1
60 plus	25	41.7	2	3.3	18	30.0	15	25.0	60	100.0

[1] Biopsies obtained within 18 months.

[2] Estimated from a 50 percent terminal digit sample.

[3] Includes probable intraepithelial carcinoma of cervix, adenocarcinoma of cervix, cancer of corpus uteri, and a few cancers of other sites. The latter 2 conditions were estimated from a 50 percent terminal digit sample.

Table 6 gives such estimates separately by age group and race. Combining all ages, the proportion was 48 percent for white and 37 percent for nonwhite women. Nine and 12 percent of white and nonwhite women, respectively, had cancer of other sites and types, including a "probable" diagnosis only. The remaining 44 percent of white and 51 percent of nonwhite women were classified either as negative or as having atypical changes. The difference between the races in the proportion with positive diagnoses is due to an excess of IEC cases in the white race. Thus, the specificity of the test, as defined in this way, is on the order of 50 percent, which compares favorably with other diagnostic screening procedures. The specificity increases with age and is especially low in women under 25. Under 45 years of age it is relatively greater for IEC than for SCC cases, and the inverse is true after age 45.

Age differences of patients and controls can produce differences in other factors, such as never marrying. To avoid these differences, patients and controls are compared within each age group by the method of "observed" and "expected" cases.

Marriage History

The procedure for calculating the expected cases (table 7) is as follows: For each race in each age group i, there are a_i cases and b_i controls, classifiable into marriage history categories 1 . . . j. There are b_{ij} controls in age group i and marriage history category j. The expected number of cases in this subgroup $e_{ij} = (a_i/b_i)\ (b_{ij})$. The age-adjusted total expected number of cases for marriage history category $j = \sum_{i=1}^{n} e_{ij}$. This method is used for obtaining all age-adjusted expected numbers in the tables. Unless otherwise stated, however, the age-specific case control ratios do not include women who are excluded from the contingency table.

The method described by Cochran (*85*) was used to combine the 2 × 2 contingency tables for each age group. Proportions p_{i1} for cases and p_{i2} for the controls were obtained in each age subgroup i. The values of $\overline{d}$, a weighted average of the differences $p_{i1} - p_{i2}$; its standard error $SE\overline{d}$; and the normal deviate $\frac{\overline{d}}{SE_{\overline{d}}}$ have been calculated and are shown in each table. The particular proportions p_{i-} used as a basis for comparison are defined. The probability of obtaining a deviate as larger or larger by random sampling variation is given.

Table 7. Observed and expected cases for women never married, by type of case and race[1]

Type of case	White[2]		Nonwhite[3]	
	Observed	Expected	Observed	Expected
Squamous cell carcinoma	0	6.5	1	3.5
Intraepithelial carcinoma	5	10.4	3	6.6

[1] Based upon age and race specific case control ratios for all women.

[2] Patients and controls compared with respect to $P_{i-} = \frac{\text{Never married}}{\text{All women in subgroup}}$

SCC $\frac{\overline{d}}{SE} = \frac{0.0517}{0.0197} = 2.62; P = 0.009$

IEC $\frac{\overline{d}}{SE} = \frac{0.0293}{0.0177} = 1.65; P = 0.099$

[3] No cases of intraepithelial or squamous cell carcinoma in nonwhite women never married nor pregnant.

Table 8. Observed and expected cases for women according to age at first marriage, by type of case and race[1] [2]

Age at first marriage	Squamous cell carcinoma		Intraepithelial carcinoma	
	Observed	Expected	Observed	Expected
White				
Total	129	128.8	177	177.0
Under 18	43	25.8	66	34.9
18–19	34	28.1	49	43.3
20–24	38	49.8	45	71.1
25 plus	14	25.1	17	27.7
Nonwhite				
Total	89	89.2	88	88.0
Under 18	37	38.0	36	38.4
18–19	30	17.3	21	22.3
20–24	15	21.6	21	20.7
25 plus	7	12.3	10	6.6

[1] With known age at first marriage.

[2] White patients and controls compared with regard to $P_{i-} = \frac{\text{Number under age 18}}{\text{Number under age 18 plus number 25 and over}}$

SCC $\frac{\overline{d}}{SE} = \frac{0.2301}{0.0704} = 3.27; P = 0.001$

IEC $\frac{\overline{d}}{SE} = \frac{0.2323}{0.0588} = 3.95; P = 0.0001$

The Cochran chi-square test (*86*) assumes that the data are subject to a binomial variation only. Consequently, the binomial proportion of total variation has been estimated for a variety of situations in which this test is used in present study. The recommended criterion of over 80 percent binomial variation was exceeded in 6 of 7 estimates, and the remaining estimate was only slightly less. We believe, therefore, that the data in the present study are suitable for using the Cochran test of significance.

Table 7 shows a deficiency of cases in white and nonwhite women with a history of never having married. Only 9 IEC and SCC cases were found compared with 27 expected. None of the 5 unmarried white patients gave a history of pregnancy compared with 3 of the 117 unmarried controls; however, all 4 unmarried nonwhite cases had been pregnant compared with 44 of 73 unmarried controls.

Table 8 gives a distribution of observed and expected cases by age at first marriage. Among white women, considerably more cases were observed than expected in those who married before age 20. No consistent association was found in nonwhite women, although an excess of SCC cases occurred in those marrying at 18 or 19 years of age.

Pregnancy History

Table 9 compares observed and expected cases among women who were never pregnant. Generally, there are fewer observed than expected cases for each category of case except for 10 white SCC patients who did not have symptoms. There are considerably fewer observed than expected cases in patients with SPC findings.

Table 10 gives the distribution of observed and expected cases by age at first pregnancy. The expected numbers are based upon

Table 9. Observed and expected cases for women never pregnant, by type of case and race[1]

Type of case	White[2]		Nonwhite[2]	
	Observed	Expected	Observed	Expected
Squamous cell carcinoma	16	24.3	11	19.4
Asymptomatic squamous cell carcinoma	10	10.0	5	7.1
Intraepithelial carcinoma	24	34.0	6	14.9
Suspicious or positive cytologic findings[3]	111	158.1	86	115.8

[1] Expected cases based upon age and race specific case control ratios for all women with known pregnancy histories.

[2] Patients and controls compared with regard to

$$P_{i.} = \frac{\text{Number never pregnant}}{\text{Number never pregnant plus number ever pregnant}}$$

White SCC $\frac{\bar{d}}{SE} = \frac{0.0690}{0.0361} = 1.91; P = 0.056$

White IEC $\frac{\bar{d}}{SE} = \frac{0.0554}{0.0298} = 1.86; P = 0.063$

White with SPC findings, excluding SCC and IEC, $\frac{\bar{d}}{SE} = \frac{0.0642}{0.0261} = 2.46; P = 0.014$

Nonwhite SCC $\frac{\bar{d}}{SE} = \frac{0.0918}{0.0458} = 2.00; P = 0.045$

Nonwhite IEC $\frac{d}{SE} = \frac{0.0991}{0.0400} = 2.48; P = 0.013$

Nonwhite with SPC findings, excluding SCC and IEC, $\frac{\bar{d}}{SE} = \frac{0.0409}{0.0272} = 1.50; P = 0.134$

[3] Estimated from all cases of some types and a 50 percent sample of others.

all women who gave a history of ever being pregnant, together with the age at first pregnancy.

In the white race there is a consistent relationship for each type of case, as more cancer was observed in women who had been pregnant at early ages. There is also a relationship in the nonwhite race for SCC cases; however, there is no deficiency of observed IEC cases for nonwhite women whose age at first pregnancy was over 20. There is an excess of IEC cases in the Negro women who were pregnant before 18 years of age, but there are fewer than expected cases among those whose first pregnancies were reported to be at 18 or 19 years of age. The relationships described for SCC cases also hold true for the patients who did not report symptoms. For all patients with SPC findings, there was a consistent association with early pregnancy.

Table 11 shows the great variation, by race, in the proportion of controls who reported that their first pregnancy occurred before 20 years of age: 29.5 percent of white controls and 69.1 percent of nonwhite con-

Table 10. Observed and expected cases for women according to age at first pregnancy[1], by type of case and race[2]

Age at first pregnancy	Squamous cell carcinoma		Asymptomatic squamous cell carcinoma[3]		Intraepithelial carcinoma		Suspicious or positive cytologic findings	
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
White								
Total	112	112.3	49	49.1	162	162.2	696	696.1
Under 18	25	10.8	10	4.6	39	15.0	157	66.7
18–19	29	21.1	18	9.1	40	28.6	160	134.3
20–24	39	46.7	15	21.3	59	75.0	277	316.0
25 and over	19	33.7	6	14.1	24	43.6	102	179.1
Nonwhite								
Total	81	81.4	31	31.1	85	85.0	552	552.0
Under 18	37	31.7	12	11.5	46	36.7	300	230.2
18–19	31	20.1	13	8.0	11	21.8	120	138.6
20–24	11	22.2	5	8.7	20	19.1	112	137.5
25 and over	2	7.4	1	2.9	8	7.4	20	45.7

[1] With known age at first pregnancy.

[2] Patients and controls compared with regard to

$$P_{i\text{-}} = \frac{\text{Number under age 18}}{\text{Number under age 18 plus number 25 and over}}$$

White SCC $\frac{\bar{d}}{SE} = \frac{0.2550}{0.0751} = 3.40; P = 0.0007$

White asymptomatic SCC $P_{i\text{-}} = \frac{0.3827}{0.1140} = 3.36; P = 0.0008$

White IEC $\frac{\bar{d}}{SE} = \frac{0.3246}{0.0636} = 5.10; P < 0.0001$

White with SPC findings, excluding SCC and IEC, $\frac{\bar{d}}{SE} = \frac{0.4172}{0.0595} = 7.01; P < 0.0001$

Nonwhite SCC $\frac{\bar{d}}{SE} = \frac{0.1334}{0.0671} = 1.99; P = 0.047$

Nonwhite with SPC findings, excluding SCC and IEC, $\frac{\bar{d}}{SE} = \frac{0.1476}{0.0445} = 3.32; P = 0.0009$

[3] Based upon age and race specific case control ratios for women reporting no symptoms.

trols who had become pregnant had done so before the age of 20.

Marriage and Pregnancy Histories

Tables 8 and 10 show that there are more cases observed than expected among white women with early marriage as well as among those with early pregnancy. To determine whether these two factors are independently associated with cevical cancer and to obtain expected cases, we adjusted for one factor. If significant differences remain between observed and expected cases, an independent association is indicated.

The procedure used in table 12 for the adjustment of age and pregnancy history follows: Cases a and controls b are kept in subgroups by age i, pregnancy history category j, and marriage history k. The expected cases, e, in any age, pregnancy, and marriage history subgroup, $e_{ijk} = (a_{ij}/b_{ij})\ (b_{ijk})$. Expected numbers adjusted for pregnancy history, $e_{ik} = \sum_{j=1}^{n} e_{ijk}$. Expected cases adjusted for age and pregnancy history, $e_k = \sum_{i=1}^{n} e_{ik}$.

In table 13, which is limited to married white women, adjustment has been carried out for age at first marriage and current age. The expected cases in a subgroup, $e_{ijk} = (a_{ik}/b_{ik})\ (b_{ijk})$. Expected numbers adjusted for marriage history, $e_{ij} = \sum_{k=1}^{n} e_{ijk}$ and $\sum_{i=1}^{n} e_{ij} = e_j$, the total number of expected cases for a pregnancy history subgroup.

Table 11. Number and percent of controls according to age at first pregnancy, by race[1]

Age at first pregnancy	Controls	
	White	Nonwhite
Total	1,289	625
Under 20 years	380	432
20 years and over	909	193
Percent first pregnant before 20 years	29.5	69.1

[1] "Unknowns" are omitted.

Table 12. Observed cases for white marriage history groups, and expected cases adjusted for pregnancy history, by type of case[1]

Marriage history	Squamous cell carcinoma		Intraepithelial carcinoma	
	Observed	Expected	Observed	Expected
Total	127	127.0	182	181.7
Age at first marriage:				
Under 18	43	41.9	66	63.4
18–19	34	28.3	49	43.2
20–24	37	37.4	45	52.6
25 and over	13	14.9	17	15.8
Never married	0	4.5	5	6.7

[1] With known marriage and pregnancy histories.

Table 13. Observed cases for white pregnancy history groups, and expected cases adjusted for marriage history, by type of case[1] [2]

Pregnancy history	Squamous cell carcinoma		Intraepithelial carcinoma	
	Observed	Expected	Observed	Expected
Total	127	127.2	177	177.2
Age at first pregnancy:				
Under 18	25	17.7	39	26.3
18–19	28	29.9	39	40.5
20–24	39	43.7	59	62.2
25 and over	19	22.8	23	29.4
Never pregnant	16	13.1	17	18.8

[1] Limited to ever married women with known pregnancy and marriage histories.

[2] Patients and controls compared with regard to

$$P_{i\cdot} = \frac{\text{Number first married and pregnant under age 18}}{\text{Number first married under age 18}}$$

IEC $\frac{\bar{d}}{\mathrm{SE}} = \frac{0.2018}{0.1034} = 1.95;\ P = 0.051$

IEC and SCC combined

$\frac{\bar{d}}{\mathrm{SE}} = \frac{0.1868}{0.0728} = 2.57;\ P = 0.010$

Table 14. Observed and expected cases for women according to number of pregnancies, by type of case and race[1] [2]

Number of pregnancies	Squamous cell carcinoma		Intraepithelial carcinoma[3]	
	Observed	Expected	Observed	Expected
White				
Total	115	115.0	163	162.9
1	22	25.1	34	41.2
2	28	30.7	46	51.5
3	28	20.8	31	32.1
4	13	14.8	24	17.3
5–6	10	14.6	18	13.1
7–9	8	6.6	9	6.4
10 plus	6	2.4	1	1.3
Nonwhite				
Total	81	81.2	85	84.7
1	13	17.3	17	21.5
2	18	17.0	20	16.7
3	11	11.4	13	13.9
4	7	6.1	7	8.7
5–6	12	10.1	17	13.0
7–9	14	10.7	10	7.8
10 plus	6	8.6	1	3.1

[1] No significant differences for SCC patients in either race.

[2] Expected cases are based on distribution of number of pregnancies for controls.

[3] Differences noted in this table for white IEC patients do not persist after adjusting for first pregnancy, as shown in table 15. No significant differences for nonwhite IEC patients.

Table 12 shows that adjustment for pregnancy history and age in the white race gives expected numbers which are almost equal to the observed cases in most marriage history categories. A possible exception is that no SCC cases are observed among unmarried women, although 4.5 cases are expected. For other categories, however, pregnancy, and especially early pregnancy, is sufficient to account for the observed association between early marriage and either IEC or SCC cases.

Table 13 is designed to see whether marital history can account for the association between pregnancy history and cervical cancer. After adjusting for age and marital history, most of the association with pregnancy history has also disappeared. An excess of cases remains among women who were first pregnant under 18 years of age as compared with those over 18. There are more IEC than SCC cases observed than expected.

There is a significant difference between both types of patients combined and controls with regard to the proportion first pregnant before and after age 18, when the comparison was limited to women who were married before 18 years of age. The data of Wynder and co-workers (*1*) also show an excess of cases in women who were first pregnant before 17 years of age, after adjusting for age and age at first marriage.

There is no deficiency of cases in the married but never pregnant group. Only 13 percent of the controls who were over 35 years of age had been married before age 20. Thus an older age at marriage can account for the slight observed shortage of cases among the married white women who were never pregnant. Untabulated data show that there were 16 SCC cases observed and 18.4 expected, adjusting only for age. There were 18 IEC cases observed with 24.6 expected, without considering the later age of marriage.

In summary, evidence suggests that there

Table 15. Observed cases of intraepithelial carcinoma for white women according to number of pregnancies and expected cases adjusted for age and pregnancy history[1] [2]

Number of pregnancies	IEC cases for white women	
	Observed	Expected
Total	159	159.6
1	33	33.4
2	44	47.4
3	31	31.2
4	23	20.0
5–6	18	16.1
7–9	9	9.4
10 plus	1	2.1

[1] Extra 2.5 percent of controls used in this adjustment erroneously included owing to double representation of women with 5 or more screenings.

[2] No significant differences in this table.

is a better association between cervical cancer and age at first pregnancy than age at first marriage. Age at first pregnancy is associated with SPC findings and SCC cases in nonwhite women. Neither IEC nor SCC cases are associated with age at first marriage in nonwhite women.

Considering that age at first marriage and age at first pregnancy are highly correlated and the slightly greater association considered to be between the latter and cervical cancer, a decision was made to use age at first pregnancy and absence of pregnancy to adjust for the factor which seems to be associated with one or both of these variables.

Number of Pregnancies

Table 14 shows observed and expected cases by race and number of pregnancies. There is a consistent but small positive association between number of pregnancies and IEC cases in the white race. There is no consistent relationship between SCC cases and the number of pregnancies in either race nor for IEC cases in the nonwhite race.

Table 15 shows the observed IEC cases in white women and expected cases adjusted for age and pregnancy history. There is no suggestion of an independent association between IEC cases and number of pregnancies after this adjustment.

The average years between pregnancies were calculated for each patient and control for whom the pregnancy histories were complete, and no consistent or large differences are noted for IEC or SCC cases in either race. These negative findings are not presented.

Age at Last Pregnancy

Table 16 shows an excess of IEC and SCC cases among white women whose last pregnancy was before age 20, but not among nonwhite women. One may ask whether the association of cancer and an early age at last pregnancy is due to the fact that women whose last pregnancy occurred early in life also had their first pregnancy at an early age. It will be seen in table 17, which limits the comparisons to white women whose age at first pregnancy was less than 20 and whose current age was 35 or over, that 12 SCC cases are observed among those whose last pregnancy was before age 20, compared with 6.4 expected cases. This excess is not statistically significant, and we are unable to affirm an independent association between either IEC or SCC cases and age at last pregnancy.

Religion

For 43 Jewish controls in the present study, there are no SCC cases and only one IEC case. We expected 4.6 SCC cases and

Table 16. Observed and expected cases for women according to age at last pregnancy, by type of case and race[1] [2]

Age at last pregnancy	Squamous cell carcinoma		Intraepithelial carcinoma	
	Observed	Expected	Observed	Expected
White[3]				
Total.....	108	108.1	157	156.9
Under 18.....	3	1.4	7	2.6
18–19.....	11	2.6	10	5.3
20–24.....	19	19.2	39	36.7
25–29.....	29	29.7	54	51.8
30–34.....	18	25.1	30	35.3
35–39.....	16	21.8	10	20.1
40 and over.....	12	8.3	7	5.1
Nonwhite[4]				
Total.....	80	80.3	85	85.1
Under 18.....	7	8.0	11	9.5
18–19.....	11	6.0	4	8.6
20–24.....	10	16.2	25	20.6
25–29.....	13	13.4	21	22.9
30–34.....	12	12.6	13	12.3
35–39.....	15	15.1	11	7.6
40 and over.....	12	9.0	0	3.6

[1] Extra 2.5 percent of controls used in this adjustment erroneously included owing to double representation of women with 5 or more screenings.

[2] With known age at first and last pregnancy.

[3] White patients and controls compared with regard to

$$P_{i.} = \frac{\text{Number under age 25}}{\text{Number under age 25 plus number 35 and over}}$$

$$\text{SCC } \frac{\bar{d}}{SE} = \frac{0.1584}{0.0702} = 2.26;\ P = 0.024$$

$$\text{IEC } \frac{\bar{d}}{SE} = \frac{0.1513}{0.0807} = 1.87;\ P = 0.062$$

[4] No significant differences in the nonwhite.

5.2 IEC cases after adjustment for age. It may also be observed in table 18 that there are an estimated 5 Jewish women with SPC findings compared with 23.3 expected. Actually, there are only three observed cases: one IEC, one negative biopsy, and one failure to have a biopsy. The latter two are doubled to estimate the five women with SPC findings. The difference between the proportion of Jewish patients and Jewish controls is significant at the 5 percent level for SCC cases but not for IEC cases nor SPC findings, excluding IEC and SCC cases. The comparisons for both SPC findings and IEC cases are between the 5 and 6 percent levels. Our findings are consistent with earlier observations and would suggest that cases of all types are deficient in Jewish women. The data in table 18 fail to show evidence that other religious affiliations are associated with cervical cancer. There are too few non-Protestant Negroes to analyze.

Table 17. Observed and expected cases for white women according to age at last pregnancy, with first pregnancy under age 20, by type of case[1]

Age at last pregnancy	Squamous cell carcinoma[2]		Intraepithelial carcinoma	
	Observed	Expected	Observed	Expected
Total	44	43.9	44	44.2
Under 20	12	6.4	10	8.3
20–29	15	16.6	18	18.0
30 and over	17	20.9	16	17.9

[1] Limited to current age 35 and over and to known ages at first and last pregnancies.

[2] Patients and controls compared with regard to

$$P_{i\cdot} = \frac{\text{Number under age 20}}{\text{Number under plus number over age 20}}$$

$$\frac{\bar{d}}{SE} = \frac{0.1187}{0.0651} = 1.82; P = 0.069$$

Socioeconomic Area

The observed and expected SCC cases and SPC findings show a consistent association with SE area (table 19). Fewer cases were observed than expected in the upper SE areas, and the reverse was true in the lower areas. The relationship to SE area was in the same direction for the IEC cases, except that the deficiency of cases was greater in area 2 than in area 1.

Table 18. Observed and expected cases for white women according to religion, by type of case[1]

Religion	Squamous cell carcinoma		Intraepithelial carcinoma		Suspicious or positive cytologic findings	
	Observed	Expected	Observed	Expected	Observed	Expected
Total	138	137.8	193	192.6	839	838.7
Protestant	105	99.3	153	141.2	636	612.9
Catholic	7	9.8	16	13.2	52	58.2
Jewish	0	4.6	1	5.2	5	23.4
Other	1	1.1	0	1.7	7	7.6
None	0	.0	0	.1	2	.7
Unknown	25	23.0	23	31.2	137	135.9

[1] Patients and controls compared with regard to

$$P_{i\cdot} = \frac{\text{Number of Jewish faith}}{\text{Number in all known religious groups}}$$

SCC $\frac{\bar{d}}{SE} = \frac{0.0386}{0.0180} = 2.14; P = 0.032$

IEC $\frac{\bar{d}}{SE} = \frac{0.0266}{0.0138} = 1.93; P = 0.054$

SPC findings, excluding SCC and IEC, $\frac{\bar{d}}{SE} = \frac{0.0227}{0.0118} = 1.92; P = 0.055$

Because of our difficulty in rating the nonwhite population on this attribute, the data for them are not presented. Fourteen indexes which describe the SE status, housing, and other characteristics of the population as determined in the 1950 census were used to compare observed and expected SCC and IEC cases for each race. In the white race a number of methods of grouping census tracts according to SE status shows large differences between observed and age-adjusted expected cases of both types. There are four that are similar in this respect. They are based upon indexes of occupation, education, cost of housing, and crowding. The groupings based upon income showed much smaller differences. This is noted here because the study of morbidity from cancer in the United States used an index based upon income (*7*).

Socioeconomic Area and Pregnancy History

Table 20 shows that early pregnancy was more common in white controls living in lower SE areas. Hence, an association between cancer and low SE status could be expected for this reason alone, and it is necessary to examine the data considering age at first pregnancy. To accomplish this the data were subdivided by pregnancy history and the relationship between each type of case and SE area was examined (table 21).

Table 20. Observed and age-adjusted expected white controls with first pregnancy under age 20, by socioeconomic area

Socioeconomic area	White controls [1 2 3]	
	Observed	Expected
Total	268	267.9
1 (highest)	26	42.2
2	48	61.6
3	129	124.9
4 (lowest)	65	39.2

[1] Computed separately by age group and added through all ages over 20.

[2] Limited to women who had been pregnant and whose age at first pregnancy was known.

[3] Controls whose age at first pregnancy was under 20 were compared with controls whose age at first pregnancy was over 20. The proportions compared were:

$$P_{i\cdot} = \frac{\text{Number in areas 1 and 2}}{\text{Number in areas 1 and 2 plus number in area 4}}$$

$$\frac{\bar{d}}{\overline{SE}} = \frac{0.3067}{0.0512} = 5.99;\ P < 0.0001$$

Table 19. Observed and expected cases for white women according to socioeconomic area, by type of case[1]

Socioeconomic area	Squamous cell carcinoma		Intraepithelial carcinoma		Suspicious or positive cytologic findings	
	Observed	Expected	Observed	Expected	Observed	Expected
Total	115	115.1	144	143.9	653	652.9
1 (highest)	9	21.7	21	26.2	66	117.5
2	26	33.3	24	38.5	135	175.9
3	57	47.8	67	61.1	316	280.6
4 (lowest)	23	12.3	32	18.1	136	78.9

[1] Patients and controls compared with regard to

$$P_{i\cdot} = \frac{\text{Number in area 1}}{\text{Number in area 1 plus number in area 4}}$$

$$\text{SCC } \frac{\bar{d}}{SE} = \frac{0.3453}{0.0937} = 3.69;\ P = 0.0002$$

$$\text{IEC } \frac{\bar{d}}{SE} = \frac{0.2024}{0.0727} = 2.78;\ P = 0.005$$

$$\text{SPC findings, excluding SCC and IEC } \frac{\bar{d}}{SE} = \frac{0.2820}{0.0666} = 4.23;\ P < 0.0001$$

Table 21. Observed and expected cases for white pregnancy history groups, by socioeconomic area and type of case

Socioeconomic area	Squamous cell carcinoma [1]		Intraepithelial carcinoma [2 3]		Suspicious or positive cytologic findings [4]	
	Observed	Expected	Observed	Expected	Observed	Expected
Total	43	42.9	57	57.1	249	249.0
First pregnancy under age 20:						
1 and 2 (highest)	5	13.2	13	15.9	46	71.3
3	22	20.1	30	25.6	124	118.4
4 (lowest)	16	9.6	14	15.6	79	59.3
Total	49	48.9	59	59.2	.....	.....
First pregnancy age 20 and over:						
1 and 2 (highest)	19	24.5	20	28.2	.....	.....
3	23	19.7	26	25.3	.....	.....
4 (lowest)	7	4.7	13	5.7	.....	.....
Total	.....	.....	.....	.....	209	208.8
First pregnancy age 20–24:						
1 and 2 (highest)	.....	.....	.....	.....	65	99.2
3	.....	.....	.....	.....	101	86.0
4 (lowest)	.....	.....	.....	.....	43	23.6
Total	.....	.....	.....	.....	75	75.0
First pregnancy age 25 and over: [5]						
1 and 2 (highest)	.....	.....	.....	.....	33	36.1
3	.....	.....	.....	.....	37	33.0
4 (lowest)	.....	.....	.....	.....	5	5.9
Total	.....	.....	.....	.....	91	91.1
Never pregnant: [5]						
1 and 2 (highest)	.....	.....	.....	.....	41	47.0
3	.....	.....	.....	.....	42	36.0
4 (lowest)	.....	.....	.....	.....	8	8.1

[1] Patients and controls compared with regard to $P_{i\cdot} = \frac{\text{Number in areas 1 and 2}}{\text{Number in areas 1 and 2 plus number in area 4}}$

SCC first pregnancy under age 20 $\frac{\bar{d}}{\text{SE}} = \frac{0.3819}{0.1200} = 3.18$; $P = 0.001$

SCC first pregnancy over age 20 $\frac{\bar{d}}{\text{SE}} = \frac{0.1038}{0.0774} = 1.34$; $P = 0.180$

[2] No significant differences in IEC women with first pregnancy under age 20.

[3] IEC with first pregnancy over age 20 $\frac{\bar{d}}{\text{SE}} = \frac{0.2251}{0.0718} = 3.14$; $P = 0.002$

[4] SPC findings, first pregnancy under age 20, excluding IEC and SCC, $\frac{\bar{d}}{\text{SE}} = \frac{0.2401}{0.0870} = 2.76$; $P = 0.006$

SPC findings, first pregnancy age 20 to 24, excluding IEC and SCC, $\frac{\bar{d}}{\text{SE}} = \frac{0.2329}{0.0767} = 3.04$; $P = 0.002$

[5] No significant differences.

The following scheme summarizes table 21 for the convenience of the reader. An especially convincing association with living in a low SE area is indicated by ++, a lesser but significant association, by +, a suggestive but not significant association by ±, and no association by 0. There is no suggestion of an association in reverse in any of the subgroups. All analyses are based upon age-adjusted comparison with the area of residence of the controls. Significance tests for SPC findings were done after excluding SCC and IEC cases.

Type of case	*Pregnancy history*	*Degree of condition is associated with residence in low SE areas*
IEC	First pregnant under age 20	0
IEC	First pregnant age 20 and over	+
SCC	First pregnant under age 20	+
SCC	First pregnant age 20 and over	±
SPC	First pregnant under age 20	++
SPC	First pregnant age group 20–24	++
SPC	First pregnant age 25 and over	0
SPC	Never pregnant	0

These findings are interpreted as meaning that after at least partially eliminating the effect of age at first pregnancy there remains an association of SPC findings and IEC and SCC cases with residence in a low SE area. There is also a definite association between each type of case and pregnancy history when the data are divided into SE areas. However, these comparisons are not shown.

Discussion

The resident women of Memphis who were examined cytologically comprise a definable population within which statistical associations have been demonstrated by comparing the characteristics of patients and controls. The validity of these findings depends on whether the identified cases and controls are representative of survey participants with regard to the factors studied. Aside from chance variation, we have no reason to believe that the controls are anything but representative of those who gave no evidence of cervical cancer.

Some cases were not diagnosed because some women did not have biopsies. However, the differences in biopsy rates by age and race do not affect the validity of the associations which have been shown, because the comparisons are adjusted for age and race. There is no other evidence that significant bias has occurred.

Because the majority of IEC patients are asymptomatic and do not have pathognomonic signs, significant bias could not enter into their selection except through differences in the proportion of patients having biopsies. Biopsy rates did not vary significantly by pregnancy history or SE area. Other reasons for failure to detect all cases are (*a*) the capacity of lesions to exfoliate cells and (*b*) laboratory errors. There would seem to be no reason why these factors should vary with regard to the characteristics studied.

We have used a more devious approach in determining that SCC cases are representative of the defined population. The bias which might have occurred when clinical SCC cases were included could have been expected to produce over-representation of cases coming from the sources which provided medical care. The fact that this was not seen for either type of cancer suggests that this type of bias did not occur.

This parallelism between IEC and SCC cases is repeated for other characteristics such as marital and pregnancy histories. The general similarity of associations found in the present study to the works of others shows that significant bias did not occur with regard to the clinical cases in our study. Additional supporting evidence is that the proportion of controls and patients reporting symptoms did not differ markedly by SE area or pregnancy history.

The histories, hastily taken by a great

variety of people, should be unbiased because they were recorded before a diagnosis was made. Only a few items were not recorded. It is likely, in some instances, that the number of pregnancies recorded may be too small and may not include miscarriages and abortions (*3*). We have no assurance that white women report an age at first pregnancy before marriage. However, for other items we have no reason to think that the frank questions asked would lead to biased answers.

The present study is thought to fill the gap between studies of unrepresentative cases such as those reported from a single hospital and morbidity studies which are representative of an entire population but which, unfortunately, describe only the simplest possible characteristics such as age, race, whether the person has ever been married, and the district of residence. Our data are less representative of an entire population than are morbidity surveys, and our histories contain less information than hospital studies, but they allow us to examine the association of cervical cancer with early marriage or pregnancy and with SE status over a wide variation of each factor.

Cytologic screening is the only practical means of describing the distribution of subclinical including IEC cases in a population. Even though all IEC cases may not proceed to invasion, the epidemiologic distribution of this lesion is of interest in its own right, since it may be analogous to a subclinical infection in communicable disease. At least some of the same etiological factors probably are operative in IEC cases and in frank carcinoma of the cervix.

The estimated sensitivity for a single vaginal cytologic examination is based upon the number of women who had a biopsy at the time of screening and who had a satisfactory initial smear. These women probably had a visible lesion of the cervix. Eighty-six percent of the SCC patients had a suspicious or positive initial smear. This figure compares favorably with reports from other laboratories that from 75 to 95 percent of clinical cases of carcinoma are detectable by this means (*87*). IEC sensitivity has been reported to be from 61 to 69 percent (*88, 89*). There is some evidence that sensitivity is higher if the epithelium of the cervical glands is diseased (*90*).

The sensitivity of the screening technique used in Memphis is greater than that for a single cytologic examination, as some cases were detected by repeat smears because the initial smear has been unsatisfactory or atypical. Fifteen percent of the SCC cases and 28 percent of the IEC cases were detected by such repeat smears in the first screening.

The quality and number of cells obtained from the cervix are superior to vaginal smears (*91*). Sensitivity for intraepithelial carcinoma has been reported to be 89 percent in a study in which cytology was not the primary method of detecting cases (*89*). While some cases were not detected in the present study because cervical specimens were not routinely obtained, the women who were examined are probably more representative because of their wider acceptance of the simpler vaginal smear technique, which was often obtained by a female technician and did not require the use of a speculum.

Direct information on virginity, divorce, promiscuity, and the circumcision status of sexual partners was not collected in the present study. Our data pertain only to evidence of nonvirginity, such as marital and pregnancy histories.

The data for white women show a consistent and strong association of IEC and SCC cases with early marriage. There is no association for nonwhite women. These divergent findings tend to confirm the variability reported by other studies with regard to this factor. Most findings for the white race agree that there is an association. Studies of the Negro women of Memphis resemble those for the Jewish and the non-Jewish white women of New York City in failing to show an association with early marriage (*64*). These findings contrast with those of Wynder (*1*), who reported an association for the Negro who married before 17 years of age.

There is some deficiency of observed IEC cases in the married women who had never been pregnant. This could be explained by later marriage of white women. Later marriage could not explain any differences

for the nonwhite women because this factor was not associated with cancer. If the role of early marriage cannot be established, some change which occurs during or after pregnancy may be significant in the genesis of cervical cancer. Anatomical relocation of the squamo-columnar junction occurs after delivery (*89*). This is the site of origin of almost all cases of intraepithelial and invasive cervical carcinoma (*89–93*). It is proximal to the external cervical os in the nulliparous cervix but is situated on the vaginal surface following delivery. The effect of the vaginal secretions and flora might be important. The acid barrier against infection is absent during the puerperium and is reduced at other times when cervical secretions are plentiful (*94*). In this connection it should be noted that semen is alkaline (*95*). The hyperplasia of squamous and glandular epithelium occurring during pregnancy is of interest, but its significance in the genesis of cervical cancer is unknown (*96*). Other changes associated with pregnancy could be relevant. The lack of an independent association with number of pregnancies is evidence against the role of pregnancy per se but does not necessarily argue against the importance of the first pregnancy. Cervical cancer, however, occurs with regularity among women who have never been pregnant (*21*).

The excess of cases in white women who were first pregnant under age 18 is also noted by Wynder (*1*). Nine percent of white non–Jewish patients and six percent of controls were first pregnant before 17 years of age, after adjustment for age at first marriage. In the Negro the proportions were 31 and 26 percent for patients and standardized controls, respectively. We are otherwise unable to dissociate early marriage and pregnancy in the present study. It is probable that an etiological role is played by one of these factors or an unknown factor which is related to both early marriage and pregnancy. Apparently cervical cancer is dissociated from early marriage and pregnancy in some populations (*31, 33*). It appears that early marriage and to a lesser extent early pregnancy are not associated with the cause or causes of cervical cancer in the Negro women of Memphis.

Failure to show an independent association with age at last pregnancy is in agreement with Wynder (*1*) and in disagreement with the strong association found by Lombard and Potter (*2*).

Our findings for white women show a definite association between SE area and each type of case. We have used an index based upon occupation because social class is thought to be most closely related to occupation. There is one study (*97*) in which income was rather poorly related to social status. When we used an index based upon income, the association between SE area and IEC and SCC cases was much less. It would be of interest to know whether Dorn and Cutler (*7*) would have shown a greater association between cervical cancer and SE area if an index of occupation had been used.

Among white controls, the age at first pregnancy, which was used to measure the factor associated with early marriage and pregnancy, was found to be earlier in the lower SE areas. While this finding was not unexpected, history of pregnancy was not sufficient to account for all of the SE selection among white women.

Unfortunately, the SE status of the Negro in Memphis was low and geographically homogeneous, and we were unable to develop measures which would allow us to test for SE differences. The excess incidence of cervical cancer in the Negroes of Memphis is consistent with the low SE status of the group as a whole (*98*).

Our data for Jewish women show deficiencies in SCC cases and SPC findings, exclusive of IEC and SCC cases, in keeping with findings of Stern and Dixon (*40*). The low but measurable incidence of cervical cancer in Jewish women would seem to indicate that marital relations, pregnancy, and poverty are not in themselves primarily responsible for this disease. Although the reason for the low rates in Jewish women is unknown it could be lack of exposure to a hypothetical carcinogenic factor—perhaps an infectious agent or a chemical carcinogen in smegma, either of which could be transmitted vene-

really. It is not now possible to decide whether circumcision or differences in sexual behavior are responsible for the favorable selection in Jewish women.

The lower mortality rates from cervical and all uterine cancer in the foreign-born women of the United States would seem to be inconsistent with their generally low SE status (*73*). The higher rates among native-born of foreign parents suggest studies to reveal why some cultural patterns seem to produce cervical cancer.

No study has suggested a difference in the frequency of cervical cancer for Catholics and Protestants. Kinsey and co-workers (*95*) found that the frequency of premarital intercourse did not differ materially between these religious groups but that it did differ greatly according to degree of religious devotion as measured by attendance at religious services. Therefore, the hypothesis that promiscuity is related to cervical cancer may be further tested by examining the degree of religious devotion.

The distribution of squamous cell carcinoma of the cervix in human populations is unique among presumed noninfectious chronic diseases. In view of its virtual absence in virgins, it would seem that this disease does not occur unless a certain factor is present and that this factor is related to sexual intercourse. Many of the factors associated with cervical cancer are more common in lower social classes: early marriage, unstable marriage (*99*), promiscuity especially without contraceptives (*95*), syphilis, and prostitution (*17*, *95*). At least some of these factors have been associated with each other. For example, early and unstable marriages are associated with promiscuous sexual behavior (*95*). It would seem, however, that early marriage is not necessarily associated with a higher risk of disease. The influence of certain ethnic groups upon sexual behavior would seem to be great (*100*) and might account for the lower incidence in Jews and the lower mortality among foreign-born Jews and Gentiles.

The epidemiologic distribution of cervical cancer suggests that of a venereal disease. Our data would seem to be consistent with this interpretation. A hypothesis of infection, alluded to by Gilliam (*47*) and stated by Pereyra (*41*), could, in our opinion, explain all the features. Other interpretations of the data are possible, and it is not known whether this venereal disease pattern is produced by a chemical carcinogen which might be present in smegma, a specific infectious agent, or some other mechanism.

The demonstration by Sprunt and Berton (*101*) that there is a strong SE gradient in the number of Döderlein's acid-producing bacilli in the vagina suggests a possible explanation for the SE gradient in cervical cancer, namely, that carcinogenic nonspecific or specific viral infection may be prevented by acid medium.

Additional studies are clearly indicated and would include searching for an oncogenic agent from the genitalia of both sexes and histories of the extramarital sexual behavior of cervical cancer patients and controls and their husbands.

Summary

This study was made to relate the etiology of cervical cancer to such factors as socioeconomic status and age at first marriage and first pregnancy. The data used are from a vaginal cytologic survey of women in Memphis, Tenn., classified according to the socioeconomic status of the census tract in which they lived.

After evaluating possible selective factors, the characteristics of a sample of women screened were compared with the characteristics of the cases detected cytologically.

These are the major findings of the study: For white women, age at first pregnancy, age at first marriage, and socioeconomic area of residence are definitely associated with histologically confirmed cases of invasive and intraepithelial carcinoma of the cervix, as well as with unconfirmed cases having suspicious and positive cytologic findings. Early pregnancy and a lower socioeconomic area of residence are independently associated with each of these categories of cancer.

For nonwhite women, age at first marriage was not associated with intraepithelial or invasive cervical cancer. Those reporting early pregnancy had more invasive cervical cancer as well as unconfirmed cases with suspicious or positive cytologic findings.

Age at first pregnancy and marriage were highly correlated. The number of pregnancies were not independently related to cancer. The data are consistent with the view that age at first pregnancy alone or in conjunction with early marriage is a determinant of cervical cancer. It is possible that some unidentified factor or factors linked with the two are of greater importance.

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Appendix

Form used to record histories when cytologic specimens were obtained.

J | F | M | A | M | J | J | A | S | O | N | D

PATIENT IDENTIFICATION

DO NOT WRITE ABOVE THIS LINE--FOR LABORATORY USE ONLY

1. NAME MRS. MISS (Last) (First) (Middle) — 2. DATE

3. ADDRESS (No. and Street) (City) (State)

(Has patient had previous cytology in connection with this study) ☐ Yes ☐ No

4. PHONE NO. — 5. AGE — 6. RACE ☐ White ☐ Negro ☐ Other — 7. RELIGION ☐ Prot. ☐ Cath. ☐ Jew. ☐ Other

PATIENT HISTORY

8. AGE AT FIRST MARRIAGE — 9. AGE AT FIRST PREGNANCY — 10. AGE AT LAST PREGNANCY — 11. TOTAL NUMBER OF PREGNANCIES

12. DATE OF LAST MENSTRUAL PERIOD — 13. ABNORMAL VAGINAL BLEEDING, BLOODY DISCHARGE OR SPOTTING ☐ Yes ☐ No If yes, duration:

14. PREVIOUS UTERINE OR PELVIC TREATMENT ☐ Yes ☐ No *If yes, check one:* ☐ Uterine radiation ☐ Hormones ☐ Pelvic surgery — Enter date of treatment and a brief description under REMARKS

SPECIMEN SUBMITTED BY

PRIVATE PHYSICIAN

15. NAME

16. ADDRESS

HOSPITAL OR CLINIC

17. NAME — 18. DEPT.

19. WARD — 20. PHYSICIAN

REMARKS:

UTERINE CYTOLOGY EXAMINATION

858 Madison Avenue

THIS SIDE FOR LABORATORY USE ONLY

1. VS ND.	DATE	SOURCE		FINDINGS
DIAG.	REPORT TO ☐ Dr. ☐ Pat.	DATE SENT	RECOMM.	
2. VS NO.	DATE	SOURCE		FINDINGS
DIAG.	REPORT TO ☐ Dr. ☐ Pat.	DATE SENT	RECOMM.	
3. VS NO.	DATE	SOURCE		FINDINGS
DIAG.	REPORT TO ☐ Dr. ☐ Pat.	DATE SENT	RECOMM.	
4. VS ND.	DATE	SOURCE		FINDINGS
DIAG.	REPORT TO ☐ Dr. ☐ Pat.	DATE SENT	RECOMM.	
TYPE SPEC.	DATE	LAB	DIAG.	
TYPE SPEC.	DATE	LAB	DIAG.	

DATE & ACTION

Table A–1. Interval between initial smear and final diagnosis of tissue, by race, type of case, and presence or absence of symptoms

Interval	Squamous cell carcinoma, without symptoms		Squamous cell carcinoma, with symptoms and unknowns		Intraepithelial carcinoma	
	Number	Percent	Number	Percent	Number	Percent
White						
Total	61	100.0	77	100.1	193	100.0
0–3 days	1	1.6	28	36.4	6	3.1
4 days–1 month	26	42.6	32	41.6	92	47.7
1–2 months	18	29.5	12	15.6	61	31.6
3–5 months	9	14.8	3	3.9	19	9.8
6 months–1 year	5	8.2	0	.0	9	4.7
1 year–18 months	2	3.3	2	2.6	6	3.1
Nonwhite						
Total	36	100.0	57	100.1	93	100.1
0–3 days	3	8.3	25	43.9	2	2.2
4 days–1 month	14	38.9	15	26.3	26	28.0
1–2 months	12	33.3	7	12.3	31	33.3
3–5 months	5	13.9	4	7.0	17	18.3
6 months–1 year	1	2.8	5	8.8	12	12.9
1 year–18 months	1	2.8	1	1.8	5	5.4

Table A–2. Number and percent of patients and controls according to presence or absence of symptoms and type of symptoms, by race and type of case

Symptoms reported	Controls		Squamous cell carcinoma		Intraepithelial carcinoma [1]	
	Number	Percent	Number	Percent	Number	Percent
White						
Total	1,708	99.9	138	99.9	193	100.1
Number reporting vaginal symptoms	181	10.6	56	40.5	31	16.1
Abnormal vaginal bleeding	147	8.6	47	34.0	21	10.9
Irregularities of menstrual period	27	1.6	7	5.1	6	3.1
Other vaginal symptoms	7	.4	2	1.4	4	2.1
No vaginal symptoms	1,336	78.2	61	44.2	147	76.2
Unknown	190	11.1	21	15.2	15	7.8
Nonwhite						
Total	764	100.0	93	100.1	93	100.0
Number reporting vaginal symptoms	71	9.2	49	52.8	11	12.0
Abnormal vaginal bleeding	55	7.1	48	51.7	8	8.6
Irregularities of menstrual period	12	1.6	1	1.1	2	2.2
Other vaginal symptoms	4	.5	0	.0	1	1.1
No vaginal symptoms	646	84.6	36	38.7	79	84.9
Unknown	47	6.2	8	8.6	3	3.2

[1] Chi-square = 4.3 comparing white patients and controls with and without vaginal symptoms. $P < 0.05$.

Table A–3. Number and percent of controls and patients with squamous cell carcinoma reporting symptoms, by age group and race[1]

Age group	Controls			Patients		
	Number with symptoms	Total known	Percent	Number with symptoms	Total known	Percent
White						
Total	181	1,518	[2]11.9	56	117	[3]47.9
20–24	28	243	11.5	0	0	.0
25–34	63	540	11.7	6	18	33.3
35–44	48	344	14.0	12	31	38.7
45–59	36	294	12.2	18	38	47.4
60 plus	6	97	6.2	20	30	66.7
Nonwhite						
Total	71	717	[4]9.9	49	85	[5]57.6
20–24	16	182	8.8	0	1	.0
25–34	23	233	9.9	3	6	50.0
35–44	21	148	14.2	13	23	56.5
45–59	11	123	8.9	19	30	63.3
60 plus	0	31	.0	14	25	56.0

[1] With known symptom status. [2] $P = 0.34$. [3] $P = 0.08$. [4] $P = 0.15$. [5] $P = 0.99$.

Table A–4. Number and percent of controls and patients with squamous cell carcinoma reporting symptoms, by pregnancy history and race[1]

Pregnancy history	Controls			Patients		
	Number with symptoms	Total known	Percent	Number with symptoms	Total known	Percent
White						
Total	181	1,518	[2]11.9	56	117	[3]47.9
Age at first pregnancy:						
Under 18	14	113	12.4	10	20	50.0
18–19	28	229	12.2	8	26	30.8
20–24	62	551	11.3	19	34	55.9
25 plus	36	273	13.2	8	14	57.1
Never pregnant	39	301	13.0	5	15	33.3
Unknown	2	51	3.9	6	8	75.0
Nonwhite						
Total	71	717	[4]9.9	49	85	[5]57.6
Age at first pregnancy:						
Under 18	26	262	9.9	22	34	64.7
18–19	12	150	8.0	16	29	55.2
20–24	13	139	9.4	4	9	44.4
25 plus	5	46	10.9	1	2	50.0
Never pregnant	15	110	13.6	6	11	54.5
Unknown	0	10	.0	0	0	.0

[1] With known symptom status. [2] $P = 0.46$. [3] $P = 0.17$. [4] $P = 0.39$. [5] $P = 0.52$.

Table A-5. Number and percent of white controls and patients with squamous cell carcinoma reporting symptoms, by socioeconomic area[1]

Socioeconomic area	Controls [2]			Patients [3]		
	Number with symptoms	Total known	Percent	Number with symptoms	Total known	Percent
Total	137	1,110	12.3	54	112	48.2
1 (highest)	20	198	10.1	2	8	25.0
2	30	283	10.6	11	23	47.8
3	72	482	14.9	30	56	53.6
4 (lowest)	15	147	10.2	11	25	44.0

[1] With known symptom status. [2] $P = 0.45$. [3] $P = 0.15$.

Table A–6. Observed and age-adjusted expected cases for white women, by source of referral[1] [2]

Source	Squamous cell carcinoma		Asymptomatic squamous cell carcinoma		Intraepithelial carcinoma	
	Observed	Expected	Observed	Expected	Observed	Expected
Total	138	138.0	61	61.0	193	193.1
Private physician	89	95.4	31	37.7	111	125.6
City of Memphis Hospital, in and out patients	5	2.3	0	1.0	4	2.8
Special clinics held in schools and housing developments	5	9.3	3	4.9	17	16.1
West Tennessee cancer clinic	2	.9	0	.4	2	.8
Special employee clinics	13	14.8	12	8.8	28	25.8
Applicants for health cards	2	1.7	1	1.0	3	2.4
Visitors to city of Memphis and health department clinics	21	12.1	13	6.3	24	16.1
Patients at other medical facilities	1	.8	1	.5	1	1.0
Navy, VA, and PHS hospitals	0	.7	0	.4	3	2.5

[1] Expected cases are based on age distribution of controls from each source and corresponding case control ratios for Memphis.
[2] See discussion in text.

Table A–7. Observed and age-adjusted expected cases for nonwhite women, by source of referral[1] [2]

Source	Squamous cell carcinoma		Asymptomatic squamous cell carcinoma		Intraepithelial carcinoma	
	Observed	Expected	Observed	Expected	Observed	Expected
Total	77	77.1	36	36.0	93	93.1
Private physician	25	20.2	4	7.6	14	16.2
City of Memphis Hospital, in and out patients	26	24.6	12	11.9	38	36.5
Special clinics held in schools and housing developments	1	1.2	1	.7	0	.6
West Tennessee cancer clinic	0	.0	1	.4	1	.3
Special employee clinics	0	2.2	0	1.0	2	3.4
Applicants for health cards	5	10.4	5	5.3	12	14.4
Visitors to city of Memphis and health department clinics	18	17.9	13	9.0	26	19.6
Patients at other medical facilities	2	.5	0	.1	0	1.7
Navy, VA, and PHS hospitals	0	.1	0	.0	0	.4

[1] Expected cases are based on age distribution of controls from each source and corresponding case control ratios for Memphis.

[2] The West Tennessee cancer clinic observed 16 SCC cases with less than 1 case expected. These are excluded from the nonwhite total squamous cell carcinomas in this table. (See discussion in text.)

Table A–8. Observed and expected cases for white women adjusted for age and pregnancy history, by source of referral[1]

Source	Squamous cell carcinoma		Asymptomatic squamous cell carcinoma		Intraepithelial carcinoma	
	Observed	Expected	Observed	Expected	Observed	Expected
Total	128	128.1	59	58.8	185	185.0
Private physician	79	80.2	29	33.5	102	111.5
City of Memphis Hospital, in and out patients	5	3.8	0	1.5	5	4.8
Special clinics held in schools and housing developments	5	9.3	3	4.4	17	15.9
West Tennessee cancer clinic	2	1.0	0	.4	2	.6
Special employee clinics	13	14.6	12	8.8	29	25.9
Applicants for health cards	2	2.6	1	1.1	3	3.2
Visitors to city of Memphis and health department clinics	21	15.0	13	8.3	23	20.3
Patients at other medical facilities	1	1.0	1	.4	1	.8
Navy, VA, and PHS hospitals	0	.6	0	.4	3	2.0

[1] Expected cases are based on age and pregnancy history distribution of controls from each source of referral and on corresponding case control ratios of all women with known pregnancy history.

Table A-9. Number and percent of women with suspicious or positive cytologic findings who did not have adequate tissue studies, by age group and race[1]

Age group	White women [2]			Nonwhite women [3]		
	Number with suspicious and positive cytology [4]	Number not having biopsies within 18 months [5]	Percent not having biopsies	Number with suspicious and positive cytology [4]	Number not having biopsies within 18 months [5]	Percent not having biopsies
Total	839	144	17.2	656	150	22.9
20–24	85	26	30.6	115	28	24.3
25–34	249	40	16.1	197	40	20.3
35–44	197	18	9.1	115	14	12.2
45–59	188	24	12.8	133	32	24.1
60 plus	120	36	30.0	96	36	37.5

[1] Minimum criterion for tissue studies was inclusion of squamo-columnar junction within 18 months of initial smear.
[2] $P < 0.001$.
[3] $P = 0.02$.
[4] Estimated from all SCC, IEC, and probable IEC cases and from a 50 percent sample of other women with suspicious or positive cytologic findings.
[5] Estimated from a 50 percent sample.

Table A–10. Number and percent of women with suspicious or positive cytologic findings who did not have adequate tissue studies, by pregnancy history and race[1]

Pregnancy history	White women [2]			Nonwhite women [3]		
	Number with suspicious and positive cytology [4]	Number not having biopsies within 18 months [5]	Percent not having biopsies	Number with suspicious and positive cytology [4]	Number not having biopsies within 18 months [5]	Percent not having biopsies
Total	839	144	17.2	656	150	22.9
Age at first pregnancy:						
Under 18	157	26	16.5	300	74	24.7
18–19	160	34	21.3	120	30	25.0
20–24	277	40	14.4	112	16	14.3
25 plus	102	12	11.8	20	4	20.0
Never pregnant	111	24	21.6	86	24	27.9
Unknown	32	8	25.0	18	2	11.1

[1] Minimum criterion for tissue studies was inclusion of squamo-columnar junction within 18 months of initial smear.
[2] $P = 0.73$.
[3] $P = 0.67$.
[4] Estimated from all SCC, IEC, and probable IEC cases and from a 50 percent sample of other women with suspicious or positive cytologic findings.
[5] Estimated from a 50 percent sample.

Table A–11. Number and percent of white women with suspicious or positive cytologic findings who did not have adequate tissue studies, by socioeconomic area[1]

Socio-economic area	White women [2]		
	Number with suspicious and positive cytology [3]	Number not having biopsies within 18 months [4]	Percent not having biopsies
Total...	653	122	18.7
1 (highest)..	66	12	18.2
2.....	135	26	19.3
3.....	316	62	19.6
4 (lowest)...	136	22	16.2

[1] Minimum criterion for tissue studies was a biopsy including squamo-columnar junction, within 18 months, of initial smear.

[2] $P = 0.74$

[3] Estimated from all SCC, IEC, and probable IEC cases and from a 50 percent sample of other women with suspicious or positive cytologic findings.

[4] Estimated from a 50 percent sample.

Table A–12. Number of patients with squamous cell carcinoma, by clinical stage, race, and age group

Age group	Clinical stage					
	I	II	III	IV	Unknown	Total
White [1] Total.....	99	25	6	0	8	138
20–24.....	0	0	0	0	0	0
25–34.....	18	2	0	0	0	20
35–44.....	29	1	1	0	2	33
45–59.....	29	10	4	0	2	45
60 plus.....	23	12	1	0	4	40
Nonwhite [2] Total.....	47	21	16	4	5	93
20–24.....	1	0	0	0	0	1
25–34.....	7	1	0	0	1	9
35–44.....	19	3	1	0	2	25
45–59.....	12	15	6	0	0	33
60 plus.....	8	2	9	4	2	25

[1] $P = 0.008$ for age, comparing stage I with stages II–IV.

[2] $P < 0.001$ for same comparison.

Table A–13. Number of patients with squamous cell carcinoma, by clinical stage, race, and pregnancy history

Pregnancy history	Clinical stage					
	I	II	III	IV	Unknown	Total
White [1] Total....	99	25	6	0	8	138
Age at first pregnancy:						
Under 18...	15	6	3	0	1	25
18–19.....	20	7	1	0	1	29
20–24.....	29	8	1	0	1	39
25 plus....	15	1	1	0	2	19
Unknown.....	6	2	0	0	2	10
Never pregnant.	14	1	0	0	1	16
Nonwhite [2] Total....	47	21	16	4	5	93
Age at first pregnancy:						
Under 18...	16	10	8	2	1	37
18–19.....	17	6	5	1	2	31
20–24.....	5	3	1	0	2	11
25 plus....	1	1	0	0	0	2
Unknown.....	1	0	0	0	0	1
Never pregnant.	7	1	2	1	0	11

[1] $P = 0.25$ for pregnancy history group, comparing stage I with stages II–IV.

[2] $P = 0.59$ for same comparison.

Table A–14. Number of white patients with squamous cell carcinoma, by clinical stage and socioeconomic area[1]

Socioeconomic area	Clinical stage					
	I	II	III	IV	Unknown	Total
Total....	83	21	5	0	6	115
1 (highest).....	6	3	0	0	0	9
2.....	22	1	1	0	2	26
3.....	41	10	3	0	3	57
4 (lowest).....	14	7	1	0	1	23

[1] $P = 0.13$, comparing stage I with stages II–IV.

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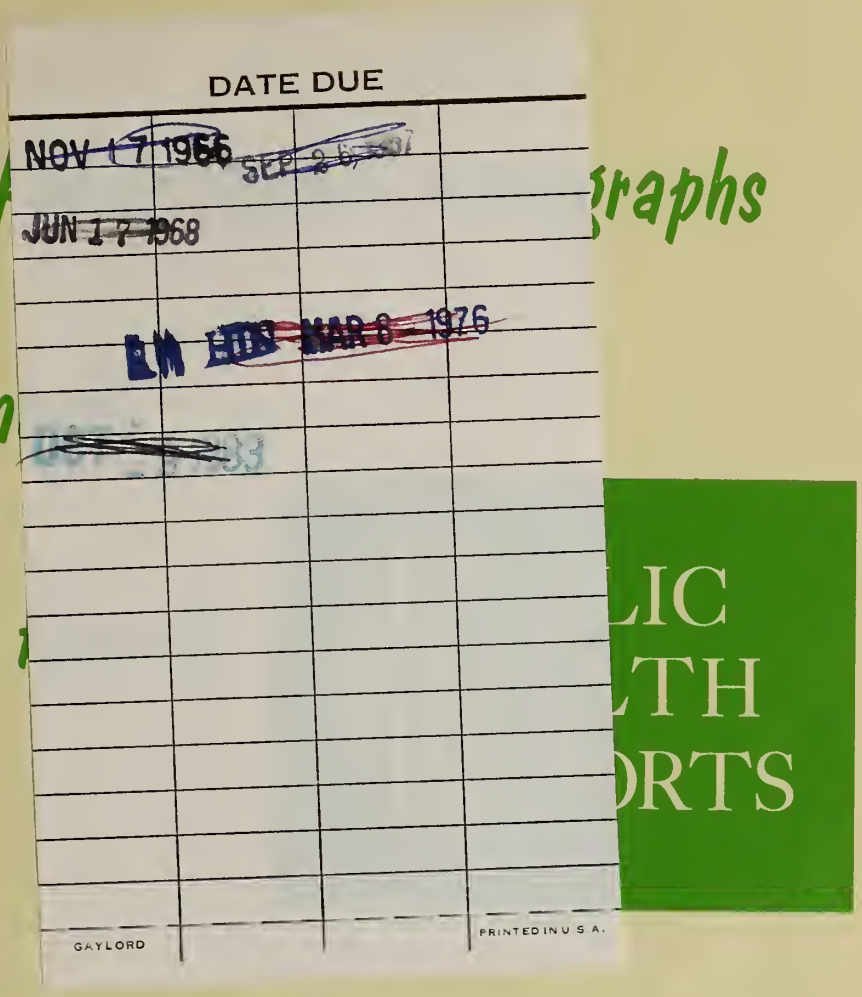

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